

AD _____

Award Number: DAMD17-02-1-0295

TITLE: An Evaluation of Stereoscopic Digital Mammography
for Earlier Detection of Breast Cancer and Reduced Rate
of Recall

PRINCIPAL INVESTIGATOR: David J. Getty, Ph.D.

CONTRACTING ORGANIZATION: BBN Technologies Solutions LLC
Cambridge, Massachusetts 02138

REPORT DATE: August 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE August 2004	3. REPORT TYPE AND DATES COVERED Annual (1 Aug 03-31 Jul 04)	
4. TITLE AND SUBTITLE An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall			5. FUNDING NUMBERS DAMD17-02-1-0295	
6. AUTHOR(S) David J. Getty, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) BBN Technologies Solutions LLC Cambridge, Massachusetts 02138 E-Mail: getty@bbn.com			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES Original contains color plates. All DTIC reproductions will be in black and white.				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) <p>The goal of this project is to evaluate stereoscopic digital mammography, compared to standard, non-stereo digital mammography, for the earlier detection of breast cancer and reduced rate of patient recall for further workup. During the project, approximately 2000 women at elevated risk for development of breast cancer will receive both standard (non-stereo) and stereo digital mammograms at the Emory Breast Clinic.</p> <p>In this second year of the project, we replaced the original CRT-based stereo display workstation with a new improved stereo workstation based on a pair of high-resolution, LCD medical monitors. The change to the new workstation has required us to rewrite the software application that will be used by the participating mammographers to control various aspects of the displayed stereo mammogram as they interpret mammographic cases. The revised software will include new capabilities that were not feasible on the original workstation. A copy of the completed stereo workstation will be shipped to Emory University in August, 2004 at which time we will begin enrolling patients into the study.</p> <p>The research protocol was changed slightly during the year. The Research Protocol and Subject Consent documents were modified accordingly and approved by both the Emory and Army IRB's.</p>				
14. SUBJECT TERMS stereoscopic digital mammography, breast cancer detection, reduced rate of recall, focal abnormality detection				15. NUMBER OF PAGES 59
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	5
Key Research Accomplishments.....	16
Reportable Outcomes.....	17
Conclusions.....	18
References.....	19
Appendices.....	21

INTRODUCTION

The objective of this project is to evaluate stereoscopic digital mammography, compared to standard, non-stereo digital mammography, for early detection of breast cancer and for reduced rate of patient recall. We hypothesize that by viewing the internal structure of the breast in depth, a mammographer will be able to detect subtle lesions in the breast earlier and with greater accuracy. When seen directly as a volumetric structure, a benign lesion may be more confidently dismissed without further workup. We also believe that the stereo mammogram will reduce false positive detections of apparent lesions, chance superimpositions of normal tissue that in the standard non-stereo mammogram resemble a volumetric focal abnormality. In the stereo mammogram, the otherwise superimposed tissue is seen as separated in depth. As a result, we believe that fewer patients will need to be recalled for further workup of what turn out to be false positives. Over the remaining three years of the project, approximately 2000 women who are at elevated risk for development of breast cancer, because of personal or family history, will be enrolled in the project and given both standard (non-stereo) and stereoscopic digital mammography screening examinations. The standard and stereo mammographic images will be interpreted in separate readings, by different mammographers. The reading data will be analyzed to determine the comparative rates of true lesion detection and cancer diagnosis, and of recall for further workup.

BODY OF REPORT

1. Overview of Year 2 Progress

We had expected to begin enrolling and imaging patients early in the second year of the project, during the fall of 2003. However, this did not occur. The primary reason was a failure of the display controller card in the stereo display workstation located at Emory University. Planar attempted to repair the card but, ultimately, was unable to effect a repair because that line of analog display controller cards, the MD series, had been discontinued and parts needed for the repair were no longer available. Fortunately, Planar had been working on the development of a new stereo display system, named StereoMirror, based on a digital display controller card and a pair of high-resolution LCD-based medical monitors. During this past project year, BBN has worked with Planar in refining the design of the prototype stereo display. One system is now in place at BBN, and a second system is being assembled and will be sent to Emory University late in August, 2004. When we have installed and tested the system, we will immediately begin enrollment of patients into the study.

We conducted a series of tests with the modified research GE digital mammography unit. We verified that a stereo mammogram acquired with a 10-degree separation between the two images (± 5 degrees) can be fused visually when viewed on the StereoMirror display, yielding an acceptable stereo image. In previous research, we had used a smaller 6-degree separation, but the 10-degree separation results in greater perceived depth within the breast tissue. However, in examining these images, which are acquired with the x-ray tube gantry off-axis, we discovered that the unit's collimator was cutting off one edge of each image. We have modified the collimator to eliminate the problem. We also acquired a series of test images on the research unit that enabled us to develop a formula relating thickness of the imaged breast tissue to the resulting amount of horizontal parallax in the stereo image pair. This information is needed to correctly invert depth in the viewed display. Finally, we have developed a means to integrate the stereo display workstation into the local area network of the Emory Radiology Department. This will permit us to move stereo mammographic images from the GE mammography unit directly to the stereo display workstation for viewing.

The replacement of the original CRT-based stereo display workstation with the newly developed LCD-based workstation has required the writing of a new display control program that will be used by the mammographers to manipulate the displayed stereo images. The new display system has some characteristics that are different from those of the earlier system. These differences are enabling us to add several new capabilities to the software that were not possible on the earlier system.

We modified the research protocol during the project year. In the original protocol, all images to be used in the stereo and non-stereo reading conditions would have been acquired on the research GE mammography unit (modified to permit off-axis image capture). However, because of the modifications, the research unit is no longer certified for clinical use and cannot be used for the standard clinical screening exam. Consequently, patients will first receive their standard screening exam on a clinically-

certified GE digital mammography unit, and then, separately, receive the stereo screening exam on the research GE digital mammography unit. This change to the protocol has been approved both by the Emory IRB and the Army HSRB.

2. Development of a New LCD-based Stereoscopic Display Workstation

During the first year of the project we built two copies of the CRT-based stereo display workstation, one of which is shown in Figure 1. One workstation was located at BBN and the other was installed at the Emory Breast Clinic at Emory University, to be used by the mammographers participating in the project. Just before we were ready to start enrolling patients into the study, the display controller card in the workstation at Emory failed. This card, a Dome MD8 card modified by Planar to support stereoscopic display, was a member of the MD series of analog display controller cards. These were no longer being manufactured by Planar, and had been replaced by a series of digital display controller cards. Planar attempted to repair the MD8 card, but found that several of the electronic components needed to effect the repair were no longer available.



Figure 1. CRT-based stereoscopic display workstation.

Fortunately, Planar was already pursuing the development of a new stereo display system, called StereoMirror, based on a Planar DX digital display controller card and a pair of their C5i medical grayscale LCD monitors. They demonstrated a prototype of the new stereo display to Dr's Getty, D'Orsi and Karellas at the RSNA meeting in December, 2003. There was agreement of all involved that the new display seemed likely to meet the needs of the stereo mammography project. The question was whether Planar could complete development and implement two of the systems, one for BBN and the other for Emory, within a matter of months. Planar kindly agreed to and met this commitment, installing the first version of the system at BBN on March 31, 2004.

The Planar StereoMirror stereo display system is shown below in Figure 2. The system consists of two LCD monitors and a glass plate, all mounted on a common horizontal axis along one edge of each component. The glass plate, which bisects the 120 degree angle between the two LCD monitors, is coated on its upper surface with a material that both transmits and reflects light (a "half-silvered" surface with 50% transmittance and 50% reflectance). The user sees the image on the lower LCD monitor transmitted through the angled glass plate, and sees the image on the upper LCD monitor reflected off the silvered coating on the top surface of the glass plate. The image projected from the lower LCD monitor is polarized in the horizontal direction, and this polarization is maintained as the image is transmitted through the glass plate. The image projected from the upper LCD is polarized in the vertical direction, and that polarization is also maintained in the image that is reflected off the glass plate. Thus, the two images, one transmitted and the other reflected, are cross-polarized. The user wears special glasses with passive, cross-polarized lenses. The lens over the Right eye is horizontally polarized and, thus, sees only the transmitted image from the lower LCD monitor. The lens over the Left eye is vertically polarized and, thus, sees only the reflected image from the upper LCD monitor. If the two images being displayed form a stereo pair, then the user is able to perceive a single fused image, seen in depth.



Figure 2. Planar StereoMirror stereo display system.

The Planar system includes a software program, Cextra, that automatically calibrates the two LCD monitors to match the DICOM grayscale standard, using luminance sensors that are built into each monitor. The program runs in the background, providing continuous monitoring and re-calibration of the two displays.

It is worth noting that the method for delivering the stereo image is different in the new system, compared to the original system. In the original CRT-based system, the two

images forming a stereo pair were displayed alternately on the same CRT face, at a high frame rate (120 Hz). The user wore active LCD glasses that served as electronic shutters, alternately opening the shutter of one eye while closing the other, and then reversing. The glasses were synchronized to the display controller card such that when the Left eye image was displayed, the Left eye shutter was open, and when the Right eye image was displayed, the Right eye shutter was open. The one advantage of this method of stereo display is that there are no image alignment issues since both images are displayed sequentially on the same monitor. On the other hand, there are a number of advantages to the StereoMirror technology. First, the LCD monitors have a much brighter luminance level (~ 500 cd/m²) compared to the CRT (~ 150 cd/m²). Dr. D'Orsi considers this increased image luminance important in digital mammography. Secondly, each image is seen *continuously* by the appropriate eye, whereas each eye sees the image only half the time using the temporal alternation methodology. The latter results in a halving of the perceived image luminance, making the luminance difference between the two technologies even larger. Also, the new digital display controller card has improved capabilities that will allow us to develop a software magnifying glass that a mammographer can apply to regions of the mammographic image, and an in-depth cursor that the mammographer can move anywhere in the displayed tissue volume to point out objects to other viewers. These capabilities could not be implemented with the original analog display controller card because of its limitations.

The first version of the StereoMirror system was installed first just at BBN and was used to develop the new software application for controlling the display, as described below in Section 3. After gaining experience with the display, Drs. Getty and Pickett met with technical and management people from Planar on May 4, 2004 to discuss several issues regarding the need for means to align the two displayed images. Ideally, if the same test image is displayed on both monitors, then the location of each image pixel should appear in exactly the same viewed location in the two displayed images. In the weeks following the meeting, Planar worked on adding hardware controls that permit more precise alignment of the two images, allowing for adjustment of multiple degrees of translational and rotational freedom. They also made the mirror and LCD monitor mounts more rugged. Finally, they substituted the state-of-the-art C5i LCD flat panels for the earlier C5 panels used in the first version, resulting in much brighter images and a much wider acceptable viewing angle. This second version of the StereoMirror display system was installed at BBN on July 6, 2004. A small amount of uncorrectable misalignment was still observed on the delivered system, and Planar said that they would pursue a further refinement of the mounting system, to be implemented before a third version of the system is sent down to Emory University late in August, 2004. The system at BBN will also be updated to the third version.

3. Stereo imaging tests on the modified GE Senographe 2000D digital mammography unit

The GE Senographe 2000D digital mammography unit that will be used to acquire stereo mammograms during the project was modified to permit acquisition of images when the x-ray tube gantry was moved off-axis so that it was no longer perpendicular to the compression table and detector. Firing the x-ray tube to acquire an image is prevented

in the clinical version of the Senographe when the x-ray tube gantry is rotated off-axis. The gantry has locking hardware detents located at 5-degree increments from the perpendicular. If we could use the plus and minus 5-degree positions of the tube for the two images of a stereo pair, we would benefit from the reproducibility and stability of the tube gantry at those detented positions. Our previous research used a smaller separation of +/- 3 degrees (6 degrees total) between the two images, so we needed to verify that +/- 5 degrees (10 degrees total) would produce a stereo pair that could be viewed successfully and without eye strain when viewed on the StereoMirror display. We acquired a stereo mammogram on one of the Emory project investigators who volunteered to have her annual screening mammogram performed on the unit. We confirmed that the stereo perception was very satisfactory when the mammogram was viewed on the new display. An added benefit of the additional separation (10 degrees versus the previous 6 degrees) was additional perceived depth in the displayed breast tissue.

However, in examining these off-axis images, we discovered that the unit's x-ray collimator was cutting off one edge of each image. This surprised us since we had not observed this effect in our earlier research that had used a prototype, pre-clinical GE Senographe 2000D unit. We have modified the research unit's collimator to eliminate the problem.

We also acquired a series of test images on the research unit that enabled us to develop a formula relating thickness of the imaged breast tissue to the resulting amount of horizontal parallax in the stereo image pair. This information is needed to correctly invert depth in the viewed display when the user requests depth inversion, as will be described more fully in Section 4 below. The tests were conducted by attaching lead BBs to the undersurface of the compression paddle and then acquiring stereo pairs of images with the compression paddle located at different heights above the table surface, from 0 mm to 80 mm. When the BB is located directly on the table surface, the horizontal separation of the BB's projection in the two images, acquired at +/- 5 degrees, is at its minimum. As the compression paddle is raised away from the table surface, the amount of horizontal separation of the BB in the two images of the stereo pair, measured in pixels of separation, increases. We fit a straight line to these measurements, and derived the following equation relating PixelSeparation (as the number of pixels), to the height of the compression paddle (in millimeters):

$$\text{PixelSeparation} = 1.8175 * \text{PaddleHeight} + 19.75$$

Finally, we have developed a means to integrate the stereo display workstation into the local area network of the Emory Radiology Department. We will make use of a software application (E-film) that will permit us to move stereo mammographic images from the GE mammography unit directly to the stereo display workstation for viewing.

4. Development of the SDM Viewer stereo display control program

We have developed a new program, SDM Viewer, to control the presentation of stereo mammograms on the StereoMirror display. The program is coded using the C++ programming language, with calls to the Planar DIMPL Class Library (DCL) to interface

to the Planar DX digital display controller card. The new program implements all of the basic functionality of the earlier program, and includes some new functions that were not possible with the earlier analog system. We describe the functionality in the sections that follow.

4.1 Stereo Image Views

A standard mammography screening exam consists of 4 images: CC and MLO views of both Right and Left breasts. Thus, a stereo screening exam will consist of 8 images, a stereo pair of images for each of the standard 4 views. The first view of a case that will be automatically constructed and presented to the mammographer is a stereo Overview image. This image will contain all four views at once, each at half-resolution. The layout of the views in the Overview image is shown below in Figure 3. The Right and Left breast CC views (and the two MLO views) are shown "back-to-back," with the chest wall at the horizontal centerline and the nipple pointing up in the R-breast images and down in the L-breast images, as if the patient were lying prone. This represents a 90-degree counter-clockwise rotation from the displayed orientation on the non-stereo clinical GE digital mammography workstation. This orientation of the displayed stereo image is dictated by the direction of movement of the x-ray tube in the patient's frontal plane when acquiring a stereo pair, and cannot be changed.

R-CC	R-MLO
L-CC	L-MLO

Figure 3. Layout of the 4 views in the Overview image

In addition to the Overview image, the mammographer will have access to each view separately, at full resolution. The orientation of the breast in each individual view will be the same as in the Overview image.

4.2 Main Screen of SDM Viewer

The main screen of SDM Viewer is shown below in Figure 4. It consists of 5 panes that address different aspects of the application. The upper left presents the mammographer with a list of patients whose stereo mammograms reside in the workstation's local database. If the mammographer highlights a patient's name, information about the patient and the mammographic exam is read from the DICOM header of the first image file and displayed in the upper right pane. If the mammographer double-clicks the patient name, or presses the "Display Case" button after highlighting the name, the mammographic images are read from the disk and a case Overview stereo image is constructed and put up on the StereoMirror display. At that point, the mammographer can move the mouse cursor from the system display sideways into the

stereo display. Once the cursor is present in the stereo display, the mammographer has full control over the patient's stereo images, as described more fully below. Once done reading the case, the mammographer can select another case for viewing by moving the mouse cursor back onto the system display and choosing another case from the list.

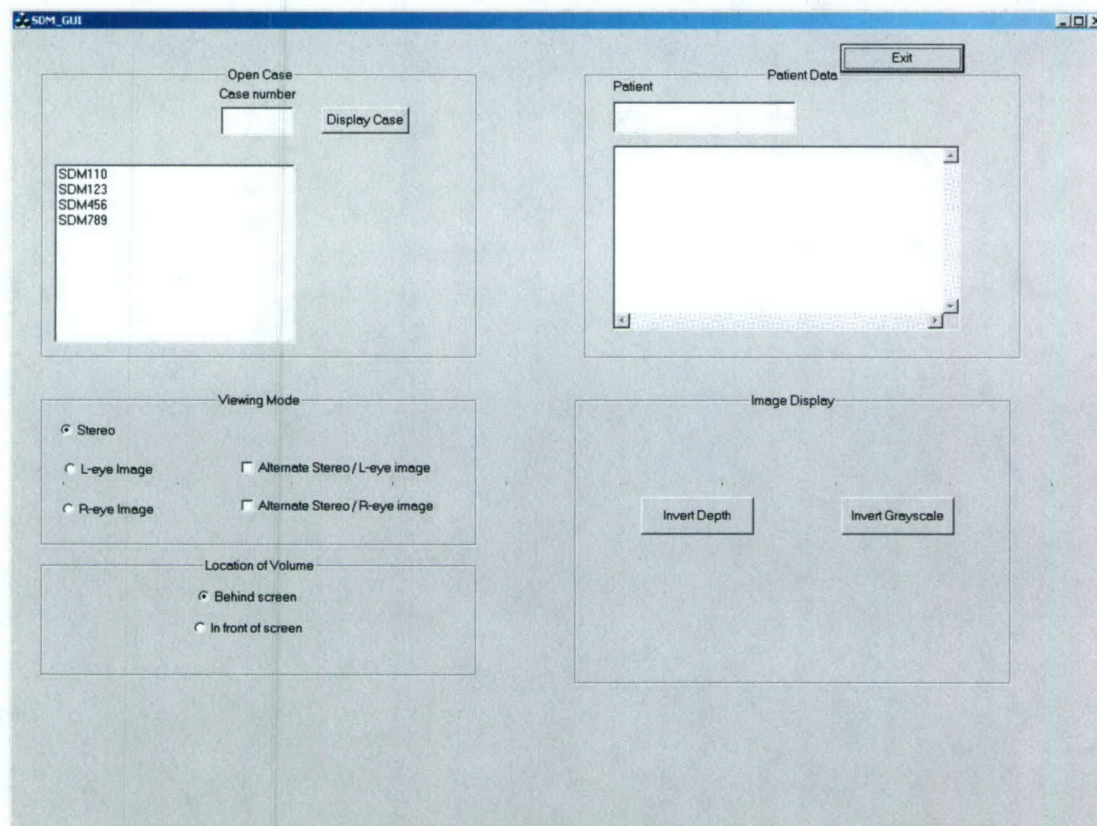


Figure 4. Main screen of the SDM Viewer display control program.

The middle left pane provides controls for the Viewing Mode for the stereo display. The default is "Stereo" viewing. However, if the mammographer wishes to contrast the stereo display with standard, non-stereo viewing, he/she can choose to view either the "L-eye image" or the "R-eye image" by itself. In this case, the same image is presented to both eyes. It is also possible, by clicking in one of the boxes to the right, to have the program cycle back and forth between stereo and non-stereo views (either the L-eye or R-eye image), switching between them every several seconds. These controls were included mostly for demonstration purposes; we do not expect the mammographer to use them in routine reading.

The pane at the bottom on the left controls the location of the displayed volume relative to the surface of the LCD display screens. The mammographer is provided with three options. The first option, the default, is to locate the displayed volume so that its depth midpoint is coincident with the LCD screen surface, with half of the displayed volume in front of the screen and half behind. This mode minimizes the absolute magnitude of the horizontal parallax seen by the viewer, providing images that are the easiest to fuse visually. The second option is to have the front surface of the displayed volume coincident with the LCD screen surface, with the volume extending back into the

display, away from the user. Users with little stereo viewing experience often find this option comfortable, but it typically results in a less dramatic sensation of depth than the other options. The third option is to have the back surface of the displayed volume coincident with the LCD screen surface, with the volume extending out into space towards the user. Stereo-experienced users often come to prefer this mode of display since it typically results in a quite dramatic sensation of depth. Location of the displayed stereo volume is implemented in the software by shifting the two images horizontally, relative to one another (See Appendix K: Getty, 2003).

The pane at the bottom on the right provides controls over how the image is displayed. The button, labeled "Invert Grayscale", causes the displayed grayscale to invert: white becomes black and black becomes white. This is accomplished in the software by complementing the entries in the display card's Look-Up-Table. The second button, labeled "Invert Depth" causes depth within the displayed volume to invert, as if one reached into a glove and pulled it inside out. Portions of the breast that had been in the background are now seen in the foreground, and vice versa. This transformation is accomplished in the program by simply swapping the Left- and Right-eye images. Mammographers find the ability to invert depth to be very helpful in that a region of interest that was originally deep in the displayed volume of breast tissue will now be at the front of the volume, perhaps making it easier to perceive. By default the imaged breast will be displayed as if viewed from above. Inverting depth will bring tissue from the lower portion of breast to the front of the displayed volume. We will display the label "Bottom" on the bottom surface of the displayed volume to indicate the location of the bottom of the breast. Inversion of depth will be apparent to the mammographer because the label will move to the front of the displayed volume. Although we have provided these controls on the main screen, they will rarely be used there by the mammographer since the functionality is duplicated by buttons on the mouse. This functionality will be more conveniently controlled by the mouse when the mammographer has moved the cursor from the system display onto the stereo display screen.

4.3 Mouse Controls

When the user moves the mouse cursor from the system display sideways onto the stereo display, particular functions are enabled on the mouse buttons. These functions are listed below.

1. Thumb button – Magnification (2X) of a local, circular region

Single click: toggles Magnification mode, in which a 3" diameter circle displays a 2X magnification of the area surrounding the current cursor position. Movement of the mouse causes corresponding movement of the magnified region.

Click and hold: Magnification mode is enabled while the button is held down and disabled when the button is released.

2. Left button – Control of displayed grayscale (inversion, brightness and contrast)

Single click: Toggles the state of Grayscale Inversion. The default is for dense tissue to display as white and air to display as black. When the grayscale is inverted, dense tissue displays as black and air displays as white.

Click and hold: Enables control of brightness (horizontal mouse movement) and contrast (vertical mouse movement). Brightness increases with horizontal movement to the right. Contrast increases with upward vertical movement. Diagonal movements of the mouse cause simultaneous changes in both brightness and contrast. The current values of brightness and contrast are frozen when the button is released.

3. Middle button and scroll wheel – Control of a stereo cursor

Single click: Toggles the Stereo Cursor mode. When enabled, the mouse cursor changes shape to a 1.5 cm ring. Movements of the mouse cause corresponding movements of the ring in the frontal plane. Movements of the scroll wheel move the ring in depth.

Scroll wheel: Moves the cursor in depth. Movement of the top of the wheel away from the user moves the cursor farther away from the user in depth. Movement of the wheel towards the user moves the cursor towards the user in depth.

4. Right button – Depth Inversion

Single click: Toggles the state of Depth Inversion. When depth is inverted, tissue that was in the background comes to the foreground, and vice versa.

4.3 Keypad Controls

The radiologist can switch among views using a small (programmable) keypad, which is visible in Figure 2 to the right of the mouse. The keys we have made available to the mammographer are shown below in Figure 5. Pressing any of the single view keys (R CC, R MLO, L CC, L MLO) brings up that single view on the display at full resolution. Pressing the “All Views” key brings up the Overview image. Pressing the “Next View” (“Prev. View”) brings up the next (previous) image in a standard repeating sequence:

All Views => R CC => R MLO => L CC => L MLO => All Views.

Low Contr.	Norm. Contr.	High Contr.	
R CC		R MLO	
L CC		L MLO	
	All Views		
Prev. View		Next View	

Figure 5. Layout of keys on the keypad.

In the DICOM header of each image file, GE stores computed parameters for an optimized grayscale Window Level and Window Width. These parameters can be used to compute values that are loaded into the display card's Look-Up-Table (LUT), such that the displayed image exhibits a standardized brightness and contrast. GE provides three sets of Window Level/Window Width values for each image, corresponding to display with Normal Contrast (the default), Low Contrast, or High Contrast. We make these three standard contrast settings available to the user on three keys on the keypad. The three Window Width parameter values are, in fact, the same across all GE images; only the Window Centers vary from image to image. Because we are displaying a stereo pair of images, we use an average of the two Window Center values when calculating values for the LUT. Similarly, for the Overview image, we average the Window Center values for all 8 contributing images.

5. Modifications to the research protocol and study forms

We made several small changes to the research protocol during the project year. In the original protocol, all images to be used in the stereo and non-stereo reading conditions would have been acquired on the GE digital mammography unit that we modified to permit off-axis image capture. However, because of the modifications, the unit is now classified as a research unit, and is no longer certified for standard clinical use. Thus, it cannot be used for the standard clinical screening exam. Consequently, patients will first receive their standard screening exam on a clinically-certified GE digital mammography unit, and then, separately, receive the stereo screening exam on the research GE digital mammography unit.

In our original study design, the reading of a stereo case would take place in two phases. In Phase I, the radiologist would have only the R MLO and L MLO views available for viewing. After completing the interpretation of the stereo MLO images, and filling out the appropriate study data forms, the radiologist would press a key to enter Phase II of the reading. In this second phase both CC and MLO views would be

available. The radiologist would then fill out a second set of study data forms. The purpose of the two-phase reading was to determine whether a single stereo view—namely, the MLO view—is sufficient for screening by itself, or whether there is added benefit in providing the CC view as well. However, in discussions with Dr. D’Orsi, we determined that the extra reading required in Phase I, including filling out a second set of forms, was going to overburden the mammographers. We therefore modified the study design to include only the second phase of reading—with all stereo views available from the start and only a single set of forms to be filled out. These changes to the protocol have been approved both by the Emory IRB and the Army HSRRB.

Since we have dropped the MLO-only reading phase from the study, we have eliminated the corresponding study form. We have added an Eligibility Checklist that will be filled out by the research administrator to verify a subject’s eligibility to be enrolled into the study. And we have added a Discrepancy Resolution form to be filled out when two mammographers meet to discuss discrepant non-stereo and stereo readings of a case. The Research Protocol, the Subject Consent form, and the full set of study forms are attached as Appendices to this report:

- Appendix A: Research Protocol
- Appendix B: Subject Consent form
- Appendix C: Eligibility Checklist
- Appendix D: Enrollment cover letter
- Appendix E: Revocation of permission letter
- Appendix F: Non-stereo reading form
- Appendix G: Stereo reading form
- Appendix H: 18-month follow-up call script
- Appendix I: 18-month follow-up call data form
- Appendix J: Discrepancy resolution form

KEY RESEARCH ACCOMPLISHMENTS (Year 2)

- Developed a new stereo display workstation based on a pair of high-resolution Planar LCD flat panel displays ("StereoMirror"). Two workstations have been assembled, one to reside at BBN and the other to reside in the Breast Imaging Clinic at Emory University.
- Developed a new software program, SDM Viewer, for the new stereo display workstation, to be used by the radiologists reading stereo mammograms.
- Modified the research GE digital mammography unit at Emory to enable acquisition of off-axis mammograms, modified the unit's collimator to eliminate image cut-off, and collected a series of test stereo images on the modified unit.
- Refined the set of study data forms to be used to collect and record data for each enrolled subject.
- Revised the Research Protocol to be followed in the project, and the Subject Consent form to be used in enrolling subjects. The modifications have been approved by both the Emory IRB and the Army HSRRB.

REPORTABLE OUTCOMES (Year 2)

PRESENTATIONS

Getty, D. J. (2003). Stereoscopic and biplane digital radiography. Special Refresher Course presentation at the meetings of the Radiological Society of North America, Chicago, November 30 - December 5, 2003.

BOOK CHAPTERS

Getty, D. J. (2003). Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography*. Berlin: Springer, 431-435.

Getty, D. J. (2003). Stereoscopic and biplane digital radiography. In E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography*. RSNA Publications, 199-209.

CONCLUSIONS

This second year of the project was devoted largely to recovering from the unexpected, irremediable failure of the CRT-based stereo display workstation at Emory University. After determining that Planar was not able to repair the failed display controller card, and that the cards were no longer being manufactured, we sought other solutions for a stereo display. Fortunately, Planar had been working on developing a flat-panel, LCD-based stereo display system, and agreed to build two high-resolution, monochrome systems as quickly as possible to support the project. Through interactions with, and feedback from, BBN project personnel, their original prototype has now gone through two iterations, each improving the quality and ruggedness of the display system. After a third set of refinements are completed, a Planar StereoMirror stereo display system will be delivered and installed at Emory University in late August. We will immediately start enrolling patients into the study and acquiring stereo mammographic images.

A second major activity during Year 2 was an almost complete rewriting of the software application, SDM Viewer, for controlling the new stereo display, necessitated by extensive differences between the old and new systems. This activity could not begin until Planar delivered the first StereoMirror system to BBN at the end of March, 2004, and has continued through the remainder of Year 2. We will benefit from the increased capabilities of the new digital display controller card, in allowing us to add functionality to the software that was not possible with the older card.

With the delivery of the second StereoMirror display system to Emory on August, 25th, we will be in a position to immediately start enrolling subjects into the study. It is unclear presently what effect the 10-month delay in the start of subject enrollment will ultimately have on the final number of subjects in the study. We will hope to achieve an accrual rate that will yield the originally anticipated number of subjects by the end of the project. We are excited to have arrived at this point in the project, and feel that the considerable superiority of the stereo images that we can see on the new stereo display more than compensates for the delay.

REFERENCES

- Abbott AH, Netherway DJ, David DJ, Brown T. Craniofacial osseous landmark determination from stereo computer tomography reconstructions. *Ann Acad Med Singapore* 1990; 19:595-604.
- Andre B, Dansereau J, Labelle H. Optimized vertical stereo base radiographic setup for the clinical three-dimensional reconstruction of the human spine. *J Biomech* 1994; 27:1023-1035.
- Doi K, Duda EE. Detectability of depth information by use of magnification stereoscopic technique in cerebral angiography. *Radiology* 1983; 146:91-95.
- Doi K, Patronas NJ, Duda EE, Geldner E, Dietz K. X-ray imaging of blood vessels to the brain by use of magnification stereoscopic technique. *Adv Neurol* 1981; 30:175-189.
- Gautsch TL, Johnson EE, Seeger LL. True three dimensional stereographic display of 3D reconstructed CT scans of the pelvis and acetabulum. *Clin Orthop* 1994:138-151.
- Getty, D. J. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography*. Berlin: Springer, 2003, 431-435.
- Getty, D. J. Stereoscopic and biplane digital radiography. In E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography*. RSNA Publications, 2003; 199-209.
- Getty DJ, Pickett RM, D'Orsi CJ. Stereoscopic digital mammography: improving detection and diagnosis of breast cancer. In: *Computer Assisted Radiology and Surgery (CARS-2001)*. Berlin, Germany: Elsevier Science B.V., 2001.
- Goodsitt MM, Chan HP, Darner KL, Hadjiiski LM. The effects of stereo shift angle, geometric magnification and display zoom on depth measurements in digital stereomammography. *Med Phys* 2002; 29:2725-2734.
- Goodsitt MM, Chan HP, Hadjiiski L. Stereomammography: evaluation of depth perception using a virtual 3D cursor. *Med Phys* 2000; 27:1305-1310.
- Graf von Keyserlingk D, De Bleser R, Poeck K. Stereographic reconstruction of human brain CT series. *Acta Anat (Basel)* 1983; 115:336-344.
- Greenwell FP. Stereo-radiography of the middle ear. *Br J Radiol* 1973; 46:159.
- Hsu J, Chalberg D, Babbs C, Pizlo Z, Delp E. Preclinical ROC studies of digital stereomammography. *IEEE Transactions in Medical Imaging* 1995; 14:318-327.

- Maidment ADA. Effects of quantum noise on dose and contrast sensitivity in stereoradiography. Medical Physics, in press.
- Pearcy MJ. Stereo radiography of lumbar spine motion. Acta Orthop Scand Suppl 1985; 212:1-45.
- Rothman SL, Allen WE, 3rd, Kier EL. Stereo roentgenography in craniofacial injuries. A revival of fundamental ideas. Radiol Clin North Am 1973; 11:683-696.
- Sekiguchi R, Satake M, Oyama H, Wakao F, Moriyama N. Stereoscopic visualization system for clinical angiography. Stud Health Technol Inform 1996; 29:690-693.
- Sexton I, Surman P. Stereoscopic and autostereoscopic display systems. IEEE Signal Processing Magazine 1999:85-99.

APPENDICES

- Appendix A: Research Protocol
- Appendix B: Subject Consent form
- Appendix C: Eligibility Checklist
- Appendix D: Enrollment cover letter
- Appendix E: Revocation of permission letter
- Appendix F: Non-stereo reading form
- Appendix G: Stereo reading form
- Appendix H: 18-month follow-up call script
- Appendix I: 18-month follow-up call data form
- Appendix J: Discrepancy resolution form
- Appendix K: Getty, D. J. (2003). Stereoscopic and biplane digital radiography. In E. Samei & M. Flynn (Eds.), RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography. RSNA Publications, 2003; 199-209.

Research Protocol

An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

1. Investigators

Principal Investigator: David J. Getty, Ph.D.
Division Scientist
BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Tel: 617-873-3751
Fax: 617-873-2794
Email: getty@bbn.com

Co-Investigators: Carl J. D'Orsi, M.D.
Director, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Mary Newell, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Kathleen Gundry, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Ronald M. Pickett, Ph.D.
Professor of Psychology
University of Massachusetts – Lowell

Medical Monitor: Ernest V. Garcia, Ph.D.
Professor and Vice Chairman for Research
Department of Radiology
Emory University

Research Coordinator: Ellen D'Orsi, R.T. (R) (M
Manager, Breast Imaging Research
Emory University

Software Engineer: Prakash Manghwani, M.S.
Staff Engineer
BBN Technologies

2. Location of Study

BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Primary Investigator: David J. Getty, Ph.D.
Division Scientist

Emory University Hospital
Breast Imaging Center
1701 Uppergate Drive
Suite C1104 WCI Bldg. 1st. flr.
Atlanta, Georgia 30322

Primary Investigator: Carl J. D'Orsi, M.D.
Director, Breast Imaging Center

3. Time Required to Complete

Expected start date: 01-August-2002
Expected completion date: 31-July-2007

4. Objectives

The primary goal of this project is to evaluate stereoscopic digital mammography, in a screening setting, for improved early detection of breast lesions, including breast cancer, and for reducing the rate of recall of patients for workup. We hypothesize that stereoscopic digital mammography, when compared with standard, non-stereo digital mammography, will:

1. Improve the detection of true focal breast abnormalities, including early breast cancer; and

2. Decrease the rate of recall of patients for further workup, by decreasing false positive readings without changing detection sensitivity.

There are three specific aims in this project. The first aim is to further develop the existing stereoscopic display system to improve its usability and efficiency for clinical use. We will observe radiologists using the stereo display and conduct interviews with them to determine ways to improve the human interface and to usefully augment its capabilities.

The second aim is to enroll approximately 500 women into the study in each of Years 2, 3, 4 and 5 of the project, for a total enrollment of about 2000 women. Women will be enrolled in the study only if they are at high risk for the development of breast cancer. Each woman will receive a screening exam consisting of a two view digital mammogram (a cranio-caudad and a medio-lateral oblique). In addition she will receive a two view stereoscopic exam consisting of two images per view (cranio-caudad and medio-lateral oblique) taken at slightly different angles.

The third aim is to conduct a controlled, paired study comparing stereoscopic digital mammography with non-stereo digital mammography for the detection of focal breast lesions and for the rate of recall for workup. Each case will be read independently by two different radiologists, one reading the stereo (research) mammograms and the other reading the non-stereo (routine clinical) mammograms. We note that we have chosen to compare stereo mammography with standard digital mammography rather than with film because it is the most direct and appropriate comparison. Support for this choice comes from a recently published study that concluded that there was no significant difference between digital mammography (using the same GE Senographe 2000D digital mammography unit that will be used in this project) and film in the rate of cancer detection.

5. Study Population

The target population for this study is women who are at high risk for the development of breast cancer. Approximately 8,800 women receive screening mammograms each year at the Emory Breast Imaging Clinic. Of these, about 10 percent, or approximately 880 women, are at high risk for development of breast cancer. We seek to enroll approximately 500 of these women at high risk in this study during each of Years 2 through 5 of the project, for a total enrollment of about 2000 patients. A sample of this size is needed to detect a practically significant difference in the rate of lesion detection between stereo and non-stereo viewing. Our reasons for using high risk as a criterion for inclusion are: 1) to maximize the number of lesions and cancers detected in the study, and 2) to provide reasonable justification for the additional x-ray imaging the patients will receive. A high-risk patient who returns for yearly or accelerated screening examinations will be eligible for multiple enrollments in the study.

The protocol for this study will be very similar to that followed in the recently published project comparing full-field digital mammography with screen-film mammography for cancer detection in a screening population. We will use the following inclusion and exclusion criteria to determine eligibility:

Inclusion Criteria

- Patient at high risk for development of breast cancer (any of the following):
 - Personal history of breast cancer, regardless of age,
 - Over 40 years of age and first-degree relative (mother, sister or daughter) with either premenopausal or bilateral breast cancer, or more than one first-degree relative with any breast cancer.
 - Positive BRCA I or II gene, regardless of age,
 - Prior benign breast biopsy that included a pathologic diagnosis of atypical lobular hyperplasia and/or lobular carcinoma in-situ, regardless of age,
 - Undergone mantle irradiation to the mediastinum for treatment of lymphoma, regardless of age.

Exclusion Criteria

- Patient does not meet any of the inclusion criteria,
- Patient has had breast augmentation, except for unilateral augmentation done for prior mastectomy,
- Patient has suspected or confirmed pregnancy,
- Patient has large breasts that cannot be adequately imaged on the 19 x 23 cm detector surface of the GE Senographe 2000D digital mammography unit.

6. **Protocol Design.** This project will use a prospective design in which each case will serve as its own control. The set of digital mammographic images acquired for a patient enrolled in the project will be used in both of the reading conditions being compared: stereoscopic reading of the two views of each breast versus non-stereoscopic, standard reading of the two views of each breast.

6a. Subject identification. The research coordinator or designee will access the already existing clinical history forms and prior mammography reports of patients scheduled for a screening mammogram. The research coordinator or designee will identify those patients who are at elevated risk, based on information on the forms and are candidates for recruitment into the study.

6b. Description of the recruitment process. The research coordinator or designee will call each scheduled patient that has been identified from the clinical history forms as being at elevated risk. The research coordinator will acknowledge and check the risk factors on the forms that are the basis of the elevated risk. It will be explained that, because of her elevated risk, she is eligible to participate in a study to evaluate a potentially better method for detecting breast cancer. The stereoscopic mammogram will be described briefly and the woman will be informed that the exam will take about 20 minutes more of her time when she comes for her routine screening mammogram and will include 4 extra mammographic images of each breast with compressions.

6c. Description of the informed consent process. Upon arrival for a scheduled mammogram, an eligible woman will be given a history questionnaire to complete. The patient will be asked if there is a chance of possible pregnancy and documentation of the patient's response will be noted on the history sheet. Possible pregnancy is an exclusion condition for the study and, in fact, for any screening mammogram. No pregnancy test will be administered. The consent form will be reviewed with the patient by the research coordinator or research technologist. At this time, any questions the woman has will be answered and, if need be, one of the radiologists involved in the study will also be available. Once both eligibility or exclusion criteria are determined and the patient agrees, two consent forms will be signed. One will be returned to the patient and the other will be kept for the study records. A copy will be made and put in the patient's medical record.

6d. Subject assignment. All of the patients enrolled in the study will be assigned for the standard digital mammogram first so a technique for the subsequent stereoscopic mammogram can be determined. Comparison of the two reading conditions being studied in the project (stereoscopic versus non-stereoscopic reading) will occur in the context of image interpretation by the radiologists.

6e. Subject screening procedures. Eligibility for admission to the study will be determined on the basis of written or verbal clinical history reviewed by the research coordinator or designee in advance of a scheduled screening mammogram.

6f. Data collection procedures. Each patient enrolled in the study will be assigned a sequential study ID number to protect patient identity. The study ID number will not include any personal identifiers (name, social security number, hospital ID number, date of birth). Only the PI of the project and the research coordinator or designee at Emory will hold master keys that relate the assigned study ID number to patient identity (name and hospital ID number). No personal identifying information will ever be disclosed in any reports or publication of this study. Five types of data will be collected on each patient enrolled in the study.

The first is the clinical history form that is part of the patient's medical record, and will be used to determine the patient's level of risk for development of breast cancer. A copy of the clinical history form will be stored in the project's research records, identified only by the subject's assigned study ID number.

The second data type is the set of standard (routine clinical) and stereoscopic (experimental) digital mammographic images. The routine clinical screening exam will consist of two views of each breast (cranio-caudad and medio-lateral oblique). The experimental stereo pair of images will be acquired by rotating the x-ray tube by approximately 10 degrees between images while the breast remains compressed. The first image will be acquired with the x-ray tube rotated clockwise by about 5 degrees from the zero angle position (perpendicular to the image receptor device) and the second image will be acquired with the x-ray tube rotated counter-clockwise by about 5 degrees from the zero angle position. A copy of the stereoscopic research digital mammographic images may also be transferred onto a CD-ROM or any other suitable electronic data

storage device for transfer to the stereo mammography viewing station. The CD-ROM will be labeled on its top surface only with the assigned study ID number. Image files are identified on the CD only with sequential serial numbers (IM1, IM2...). No personal identifying information will be used in the filenames. After the radiologist's interpretation of a case at Emory, the CD-ROM may be sent to BBN for stereo image quality monitoring and for evaluation in making further improvements to the stereo imaging workstation.

The third data type are the two mammography BI-RADS report forms, one filled out electronically by the radiologist reading the standard non-stereo digital mammograms and the other filled out by the second radiologist reading the stereo mammograms. These will become part of the patient's medical record. A copy of these forms will be printed out for the project's research records. These copies will be identified only by the assigned study ID number.

The fourth data type is a form filled out by the radiologist after completing the reading of a case in either the stereo or non-stereo reading condition. The radiologist will record on this form a quantitative judgment of the likelihood that a finding is a true focal abnormality, and a second judgment of the likelihood that a finding is cancer. This form will be identified only with the assigned study ID number.

The fifth data type is the form to be filled out by the research coordinator or designee when talking to subjects at the 18-month follow-up phone call. The purpose of this phone call is to determine whether the subject has had any more recent breast examinations since the stereo imaging study and, if so, what the outcome was. Although the coordinator must necessarily know the patient's name and phone number to make the call, the form that will become part of the study records will be identified only by the assigned study ID number.

All research records for the subjects will be kept in the research coordinator's locked office at Emory. A copy of the several study forms collected for each subject and the CD-ROM containing the stereo images will be sent to BBN, each identified only with the assigned study ID number. These mailings will be addressed directly to David Getty, the PI, and labeled as "Confidential." At BBN, the data will be entered into a computer database for analysis. The only identification of subjects in the database will be by the assigned study ID number. The CD-ROMs and research records will be kept in a locked office under the control of the PI. The computer database will reside in a password-protected computer in the PI's locked office.

The master key list linking the subjects' personal identification information with the assigned study ID codes will be kept in the Emory research coordinator's locked office, separate from all other study records and accessible only by the research coordinator. A copy of this list will also be kept in Dr. Getty's locked office at BBN, again separate from all other study records and accessible only by Dr. Getty.

The research and clinical mammographic images may be used by the investigators in scientific publications, posters, conferences and for teaching purposes. These images may also be given to other researchers within Emory University and at other

establishments who may need them for scientific purposes. The clinical and experimental images may be displayed at scientific presentations that are open to the public and they may also be posted electronically on the worldwide web. However, all images that may be used for the above stated purposes will be completely de-identified and it will not be possible to trace the identity of any patient from any of these images.

Agencies that have a right to examine patient records collected in this study include the Emory Institutional Review Board, BBN Technologies, and the U.S. Food and Drug Administration. In addition, representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

6g. Clinical assessments. The primary clinical assessment of the patient may come from the standard reading of the non-stereo digital mammograms and from the additional reading, by a different radiologist, of the stereo digital mammograms. Assignment of each participating radiologist to the two reading conditions will be counterbalanced across patients. The reading of the stereo mammograms will have the potential of contributing to the patient's current diagnosis if something is seen in the stereo mammogram that was not seen in the standard mammogram. Any finding, seen in either reading condition, will be acted upon as appropriate. The inclusion or exclusion of findings in the clinical report will be determined by the consensus of a periodic meeting of both involved radiologists after the third and fourth data points are completed for each patient. Each patient will be called at about 18 months following stereo imaging to determine outcomes so as to score the contributions of stereo mammography to the accuracy and efficacy of diagnosis.

6h. Data analysis. Truth for each reported finding will be established from imaging workup, biopsy results or 18-month follow-up. Two types of truth will be determined. First, we will determine *lesion truth*: whether or not the reported finding is a true focal abnormality. Lesion truth will be determined either from imaging workup (film studies using spot compression, magnification or other views, and/or ultrasound examination), follow-up examinations, or from biopsy results. Second, for each confirmed focal abnormality, we will determine *cancer truth*: whether the finding is malignant or benign. Cancer truth will be established either from a biopsy or from follow-up phone call 18 months after imaging. All cases, where a confirmed focal abnormality was not deemed worrisome enough to be sent to biopsy, will be followed at 18 months to confirm whether that focal abnormality was truly negative for cancer.

We will conduct several analyses of the collected data. First, using standard ROC methods, we will compare the performance of stereoscopic digital mammography to non-stereo digital mammography for detection of breast lesions. The set of confirmed lesions to be used in this, and other, analyses will be the union of all findings reported in either the stereo reading condition or the non-stereo reading condition, or in both. A finding that is reported in one reading condition, but not the other, will be scored as a zero on the rating scales (likelihood of a true lesion and likelihood of cancer) for the reading condition in which the finding was not reported. ROC curves will be fitted to the judgments made independently in each of the two reading conditions. We will compute A_z , the area under the ROC curve, as a measure of accuracy for each fitted ROC.

Statistical analysis will be conducted on the difference between the A_z computed for each reading condition, using ROC methods that account for the correlation induced by the same case set being read in the two different conditions.

Similar ROC analyses will be applied to the judgments of the likelihood of cancer. Statistical analysis of the difference between the A_z 's computed for stereo digital mammography and non-stereo digital mammography will be completed to determine if there is a difference in the cancer detection rate.

We will examine the frequency of recommended recall of patients for further workup or biopsy based on the BI-RADS classifications (classifications of 0, 4 or 5) obtained from each reading condition. Statistical analysis of the difference in this frequency for the two conditions will be conducted on the 2 x 2 table of frequencies using chi-square tests. In a related analysis, we will also construct an ROC curve for each condition using the BI-RADS classifications as a rating scale, ordered by increasing suspicion of malignancy as 1 (negative), 2 (benign), 3 (probably benign), 0 (need additional imaging evaluation), 4 (suspicious abnormality), 5 (highly suggestive of malignancy). By statistically comparing the two fitted ROC curves, we will determine whether there is a difference between the stereo and non-stereo readings in the predictive accuracy of recalling a patient for workup or biopsy.

7. Risks/Benefits Assessment

7a. Risks. There is no additional risk of physical injury in acquiring the stereo mammogram beyond that associated with a standard mammogram. There is the minimal risk of physical injury in the normal procedure of positioning and taking a mammogram. A compression paddle will be used to flatten the breast to a uniform thickness for the images. There is the risk that some bruising could occur due to the compression; this is the same risk as for the routine mammogram.

As a result of this study, participants will be subjected to a small additional amount of radiation. A typical technique will be: 26 KVP, 100 mA, and one-second exposure. A higher mAs will be used for more dense breasts, but the technique used will be about the same as with conventional film-screen imaging. The kVp utilized may vary by about ± 3 kVp depending on the thickness of the breast; this is standard practice in mammography. The x-ray beam will be restricted to the general area of interest. The average glandular dose received by the breast from each mammographic x-ray view will be approximately 160 mrad. This is about the same radiation dose given to patients in routine film mammography. This dose is approximately half the maximum dose of 300 mrad (mean glandular) recommended by the American College of Radiology (ACR) for a single-view mammogram. The Total Body Effective Dose Equivalent per image will be 8 mrem, or 32 mrem total for the four extra images per breast specified by the experimental protocol.

As part of the routine mammographic examination, the patient will be interviewed by the x-ray technologist with regard to pregnancy. In current routine practice, premenopausal patients are asked whether they are pregnant, or trying to become pregnant. The majority of this group gives a negative response to this question, and mammography is performed in the usual manner. It should be noted that there is always

a small theoretical probability that a woman in this group was pregnant and had both the standard and stereoscopic mammogram. Because of the very low energy of the x-ray beam, even in the case of the pregnancy, the dose to the fetus would be very close to the natural background radiation. Patients who are pregnant or trying to become pregnant will be excluded. As in routine mammography, we expect that most of the subjects will be beyond their childbearing years. Screening for pregnancy will be done only by asking questions and not by any blood or urine tests. It is also possible that additional evaluations which turn out to be negative or benign, may take place because of the addition of the stereoscopic mammogram.

7b. Benefits. An individual participant may directly benefit from the stereo mammography examination if additional information is detected in the reading of the stereo mammogram that is not seen in the standard, non-stereo reading. In this case, further workup of the patient would occur using standard, approved procedures. In general, however, this research project is not intended to directly benefit the individual participants. But, the information collected in this study may lead to significant improvements in the earlier detection of breast cancer through the use of stereoscopic digital mammography. The results of this research could eventually benefit all women undergoing mammography.

7c. Compensation. Subjects consenting to take part in this study will not receive any compensation for their participation.

7d. Voluntary Participation/Withdrawal. A subject's participation in this study is entirely voluntary. A woman who is invited to participate may decline without prejudice. Likewise, a subject who has enrolled in the study may choose to drop out at any time. The decision to decline enrollment or to drop out will have no effect on the woman's current or future medical care or any benefits to which she is otherwise entitled. If a woman drops out of the study, her study records will be excluded from all further review and analysis.

Under unusual circumstances, the investigator may choose to terminate an enrolled subject's participation in the study. Such circumstances might include equipment failure, discovery of an exclusion condition not evident at the time of enrollment, or development of a medical condition that precludes participation.

8. Reporting of Serious or Unexpected Adverse Events

Every patient will be carefully monitored and closely followed during the imaging procedure. Carl J. D'Orsi, M.D., FACR, will be monitoring all phases of the study as they apply to Emory University. Dr. D'Orsi will be actively involved in all aspects of this study and will be available to assist if any medical emergency should arise. Dr. Andrew Karellas is the Director of Radiologic Physics and will monitor all equipment as it applies to this study. Dr. Ernest Garcia, Ph.D. will serve as the medical monitor assigned to this study.

Adverse experiences that are both serious and unexpected will be immediately reported to the Emory University IRB and by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165)

and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days, sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

9. Disposition of Data

The digital mammographic images will be stored in the RADSTOR image archiving system, as part of the patient's medical record. The copy of the stereo digital mammograms written on a CD-ROM, and identified only by the assigned study ID number, will be retained at BBN throughout the duration of the project and for 3 years following.

The data forms, identified only by study ID, will be retained through the period of the project at both Emory University and BBN and may be destroyed at the study closure. However, the data contained on the forms will be transferred during the project to the database maintained at BBN. At termination of the project the database will be written onto CD-ROM. One copy of the database CD-ROM will be kept at BBN and another copy sent to Emory. There will be no personal identifying information in the database. The master key list linking study ID numbers to subject personal identifiers will be kept at Emory University for 3 years beyond the termination of the project.

The database CD, mammographic images CDs, and the master key list may be destroyed 3 years after termination of the project.

10. Modification of the Protocol

Proposed modifications or amendments to the protocol will be submitted to the Emory IRB and to the HSRRB for review and approval prior to implementation.

11. Departure from the Protocol

Should any departure from the approved protocol be deemed necessary due to unforeseen events, the Emory IRB and the HSRRB will be notified of the nature of the deviation, the reasons for its occurrence, and the proposed remedy, if appropriate, for review and approval prior to implementation.

12. Roles and Responsibilities of Study Personnel

BBN Consultant

David J. Getty, Ph.D., is Division Scientist at BBN Technologies and will serve as Principal Investigator for the project. As PI, he will provide oversight of the ongoing activities of the project at BBN and at Emory University. He will have primary responsibility for the further development and refinement of the stereo display system that will take place at BBN. He will be responsible for overseeing the design of the electronic database, the design of data collection forms. He will have primary responsibility for carrying out planned analyses of the data comparing reading of the stereo mammograms with reading of the non-stereo mammograms. He will have primary responsibility for preparing the annual reports for the Army, and for presenting the results of the project at scientific meetings and in publications.

Prakash Manghwani, M.S. (Computer and Information Science), is a Staff Engineer at BBN. Mr. Manghwani is a highly experienced programmer who will be responsible for writing the software application that controls the stereoscopic display system. The goal of this effort is to develop an application that permits a radiologist to manipulate the appearance of a stereo mammogram in well human-factored ways that are powerful, convenient and efficient in a clinical setting. The application will be refined iteratively as we receive feedback from radiologists using the system over the course of the project.

BBN Consultant

Ronald M. Pickett, Ph.D., is a Professor of Psychology at the University of Massachusetts—Lowell. He has worked closely with Dr. Getty on related radiological imaging projects for the past 25 years. He is an expert on human visual perception experimental design, and ROC analysis methods. He will consult throughout the project in all of these areas: helping to improve the human factors of the stereo display system to maximize information provided to the radiologist, helping to design the reading study comparing the stereo and non-stereo reading conditions, and helping in the choice of the methods of data analysis and result interpretation.

Emory University

Carl J. D'Orsi, M.D., is Director of the Breast Imaging Clinic at Emory University. He will serve as primary investigator of the clinical portion of the project conducted at Emory University, with responsibility for overseeing the enrollment of patients into the project, acquisition of stereoscopic digital mammograms on those patients, reading of the non-stereo and stereo mammograms by participating radiologists, and entry of the collected data into the electronic database. Dr. D'Orsi is a renowned radiologist with an international reputation in mammography. He has worked with Dr. Getty on medical projects for more than 20 years. He will also work with Dr. Getty in designing the data collection forms and database to be used in the project, and in the interpretation of the study results.

Mary Newell, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Kathleen Gundry, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Ellen D'Orsi, R.T. (R) (M) is Manager of Breast Imaging Research at Emory University. She will be responsible for:

- Overseeing the recruitment process and for obtaining informed consent.
- Enter clinical history and radiologic reading data into the data base.
- Assigning and maintaining the study ID numbers.
- Sending data and transmission of digital images to BBN.
- Insuring that studies are read according to the established time frame of 7 days.
- Facilitating appointments for additional imaging.
- Dealing with any concerns or complaints from study participants.

Andrew Karellas, Ph.D., is a professor of radiology and director of Medical Physics in the Department of Radiology at Emory. Dr. Karellas is an expert in the physical aspects of x-ray imaging with particular expertise in mammography. He will be responsible for the monitoring of the x-ray equipment that will be used in this project.

Ernest Garcia, Ph.D., is assigned the role of Medical Monitor for this project. He will be responsible for monitoring the care provided to enrolled patients, and arranging any necessary medical care to any enrolled patient who experiences any serious and unexpected event that occur as part of the study. He will review any such event and provide a written report within 3 calendar days of the initial report. This report will be forwarded to the USAMRMC.

**Emory University School of Medicine
Department of Radiology
Consent to be a Research Subject**

Title: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

Sponsor: Department of Defense Breast Cancer Research Program

Principal Investigator: Carl J. D'Orsi, MD

Co-Investigator: Mary Newell, MD
Kathleen Gundry, MD
Stephanie Roberson, MD

Introduction/Purpose: You are being asked to take part in a research study. You have been asked because you are scheduled to have your annual screening mammogram and you are high risk for the development of breast cancer. This study will compare two different ways of doing a mammogram, a standard digital mammogram vs. a stereoscopic digital mammogram. Both these exams involve radiation (x-rays). The stereo mammogram enables the radiologist to see the breast tissue in depth, as a 3D image. It does require a very small amount of additional radiation. The digital mammogram is your standard screening method; it is not research. It is hoped that the stereo mammogram will reveal true, breast tumors at an earlier stage, and decrease the number of patients who have to come back for repeat mammograms when an abnormal area is seen at screening. You will not receive results from your standard mammogram today as a report cannot be issued until both exams are read and each exam will be read by a different radiologist, at different times. Taking part in this study will require about 20 minutes of your time today. About 5 minutes of that time will be answering some questions about your medical history. Approximately 18 months from now, someone from the Breast Imaging research staff will contact you by phone to see if you have had any problems or further tests (biopsies, ultrasounds, mammograms, surgeries) on your breasts. This phone call will take about 5 minutes of your time. If other tests have been done, we would like copies of those reports.

The total enrollment for this study is 2000 women, all to be done at Emory University Hospital's Breast Imaging Center.

Procedures: If you agree to take part in this study, your mammogram will be done by both methods at the same appointment. The routine digital mammogram will be done first. Your breasts will be positioned and compressed, one at a time on the mammography unit. The standard two views will be taken. You will then be moved to the research room for the stereoscopic research mammogram. You will be positioned and compressed in the same way as for the routine digital exam. Two views will be done on each breast just as before. The only difference

is that there will be two exposures per view, for a total of four exposures per breast for the research mammogram. A radiologist will read the stereoscopic images at a specially de-signed stereo-display workstation while wearing stereo-viewing glasses. The reading of those images will be compared to the reading of the standard digital images, read previously by a different radiologist.

Your Doctor will receive a report based on all the available information. You will receive a letter or phone call from the Breast Imaging Center in approximately 7 business days concerning your results. If any abnormalities are found, you will be called back for further work-up. Should you need to have further work-up or an area biopsied (needle inserted and tissue taken out), we are asking your permission to review your medical records and test results.

Risks: If you take part in this research, you will have a medical imaging study that uses radiation. The test you will have includes ordinary x-rays. To give you an idea about how much radiation you will receive, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year from the natural environment. Some of this radiation comes from space and some from naturally occurring radioactivity in the soil, food and air. For the average patient, this research procedure delivers to the body the equivalent of less than 3 extra months' worth of natural background radiation. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. Radiation exposure can potentially increase your chance of developing cancer. The risk is very small, and may even be zero for the radiation exposure from this study. Pregnant women may not participate in this study due to the possible risks of radiation exposure to the fetus. Since any findings, either on the routine digital mammogram or on the experimental digital stereoscopic mammogram may be evaluated, you could possibly have additional tests and/or breast biopsies that may not have happened if you did not participate in this study.

Benefits: Taking part in this research study may not benefit you personally, but we [doctors, researchers and scientists] may learn new things that will help others. It is also possible that a biopsy requested because of your participation in this study leads to detection of early breast cancer.

Alternatives: You may choose to not take part in this study and just have your standard screening mammogram.

Compensation and Cost: You will not be paid to take part in this study. Your standard digital mammogram and any additional follow-up will be billed to you or your insurance. There is no charge to you for the research stereoscopic mammogram. We will arrange for emergency care if you are injured by this research. However, Emory University has not set aside funds to pay for this care or to compensate you if a mishap occurs. Your insurance may be billed for any

medical care provided by Emory University, but Emory will not bill you for research-related medical expenses that are not covered by insurance (for example, deductibles or co-pays), or for these expenses if you are uninsured. You or your insurance companies are responsible for paying for any medical care provided by sources other than Emory University. You should also understand that this is not a waiver or release of your legal rights. If you believe you have been injured by this research, you should contact Carl J. D'Orsi, MD at 404-778-4446.

Voluntary Participation/Withdrawal: Your participation is completely voluntary and you have the right to refuse to be in this study. You can stop at anytime after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled. The study doctor/investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest, or if you do not follow study instructions.

Contact Persons: If you have any questions about this study or if you feel being in this study has harmed you, contact Carl J. D'Orsi, MD at 404-778-4446. If you have any questions or concerns about your rights as a participant in this research study, contact James W. Keller, MD, Chairman of the Emory Institutional Review Board at 404-727-5646.

New Findings: We may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information.

Confidentiality (Protection) of Your Research Records: You will be assigned a study ID number that will be used on all study records. The study ID number will not include any personal identifiers, such as your name, social security number, medical record number, or date of birth. All study records at Emory will be kept in the Research Coordinator's locked office.

The study's Research Coordinator at Emory will keep a master list that links your identity to your assigned study ID number. This master list will be kept in a separate file in the Research Coordinator's locked office. The project's Principle Investigator at BBN Technologies will also keep a copy of this master list in a separate file in his locked office. Only the Emory Research Coordinator and designated Breast Imaging research staff and the Principle Investigator at BBN Technologies will have access to the master lists. The master list will be kept for at least 5 years after the termination of the study.

The data forms generated in this study and the stereoscopic mammographic images that will be stored on a CD-ROM will be identified only by your assigned study ID number. No personal identifiers will be used. Copies of these forms and the mammographic images will be sent to BBN Technologies for analysis,

identified only by your study ID number. At BBN, a computer database will be developed to analyze the data. Study participants will be identified in the database only by study ID numbers. The database will be kept in a password-protected computer. All study records at BBN, including the digital mammographic images that will be stored on a CD-ROM, will be kept in a locked room controlled by the project's Principle Investigator.

People from the Emory University Institutional Review Board (IRB), Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), BBN Technologies and representatives of the U. S. Army Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects.

We will not use or disclose your records in any ways other than those described in this form, and we will keep your records private to the extent allowed by law. We will do this even if outside review of your records occurs. Your name and other facts that might point to you will not appear when we present this study or publish its results.

The research and clinical mammographic images may be used by the investigators in scientific publications, posters, conferences, and for teaching purposes. These images may also be given to other researchers within Emory University and at other establishments who may need them for scientific purposes. The clinical and experimental images may be displayed at scientific presentations that are open to the public and they may also be posted electronically on the worldwide web. However, all images that may be used for the above stated purposes will be completely de-identified and it will not be possible to trace your identity from any of these images.

Protected Health Information (PHI): Protected health information (PHI) is any health information provided to persons that identifies you or information that can reasonably be used to identify you. The people who are conducting this study (the "Researchers") may need to look at your medical records that contain this PHI. In addition, government agencies that make rules and policies about how research is done, including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) and, have the right to review these records. Sponsors who pay for the study, the Emory University Institutional Review Board (IRB) and the U. S. Army Research and Materiel Command also have the right to review your medical records. In addition, these records may be disclosed pursuant to court order.

Under the Health Insurance Portability and Accountability Act (HIPAA), a federal law enacted to protect the privacy of your PHI, before we can use or disclose your PHI, we must provide you with information about what PHI will be used for this research study and how it will be used and disclosed. This section of this form provides you with this information regarding your PHI. Specifically, it will tell

you what PHI the Researchers will look at; who will collect the PHI; who will use the PHI, with whom it will be shared and the purpose of each use or disclosure; the expiration date or event, if any, after which we won't use or disclose your PHI any more; and your rights under HIPAA to ask us not to use your PHI any more. If you decide to participate in this research, then you will be agreeing to let the Researchers and any other persons, companies or agencies described below to use and share your PHI for the study in the ways that are set forth in this section, so please review this section very carefully.

What PHI will the Research Team Use: As part of your clinical care, the Researchers will look at information that identifies you such as your name, patient identification number, medical records number, birth date and social security number. The Researchers will also look at your medical history and at any results from laboratory tests and physical examinations that you have had performed. In addition, if you have a bad outcome or 'adverse event' then the Researchers may also need to look at your entire medical record.

Who will collect the PHI: The Researchers will collect and copy the PHI described above. If any of the PHI is to be shared with other persons, as described later on in this section, then the Researchers also will be responsible for making these disclosures.

Who will Use the PHI; With Whom will it be Shared; and For What Purpose(s) Will it be Used or Shared: In order to conduct the study, the PHI that is collected regarding you will be used by or shared with the following persons, agencies or companies for the purposes listed in the chart below.

Person/Entity	Purpose
Researchers at Emory and BBN Technologies	To conduct the study entitled, "An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall."
Governmental Agencies with oversight over the research being conducted, including the FDA and OHRP	To monitor safety, efficacy and compliance with applicable laws and regulations.
University personnel, committees and departments charged with oversight of research, including the IRB.	To monitor safety and compliance with applicable laws, regulations and University policies and procedures.
Representatives of the US Army Medical Research and Material Command, the study sponsors.	To provide oversight for the study and as part of their responsibility to protect human subjects.

Expiration Date or Event: The Researchers will continue to use your PHI until the study is closed and the period for which any records relating to the study must be retained has ended.

Your Right Under HIPAA to Revoke Your Authorization and Ask Us Not to Use Your PHI Any More: Giving the Researchers your authorization to use and share your PHI is voluntary. At any time, you may choose to revoke your authorization for the Researchers to use and share your PHI. If you revoke your authorization, the Researchers may no longer be able to provide you with any research-related treatment, but your revocation will not otherwise affect your current or future health care. Further, if you revoke your authorization, there will be no penalty or loss of any benefits to which you are otherwise entitled. If you decide that you want to revoke your authorization for us to use your PHI, you may do so by completing and signing the revocation letter that you receive with your copy of this Combined Informed Consent/HIPAA Authorization form and providing it to the researcher. If at any time you need another copy of this form, you may ask the Researchers to provide you with one. Once we receive your written revocation of your authorization to use your PHI, we will not make any other use of your PHI or share it with anyone else, except as follows: (a) we will let the study sponsor know that you have revoked your authorization; (b) we will not ask the study sponsor or any other parties to whom we said we would disclose data to return any data that we provided to it/them before you revoked your authorization; (c) and, even after we receive your revocation, we will still provide the study sponsor and any other parties to whom we stated that we would disclose data with any data that is necessary to preserve the integrity of the research study, and we will provide any governmental or University personnel, departments or committees with any data that they may need in order to comply with/or investigate adverse events or non-compliance with any applicable laws, regulations or University policies.

PHI May be Re-disclosed: If we disclose your PHI to one of the other parties described above, that party might further disclose your PHI to another party. If your PHI is further disclosed, then the information is no longer covered by HIPAA.

Signature and Date: The Researchers will ask you to sign and date this form. A copy of your signed and dated consent/authorization will be placed in your medical record(s).

We will give you a copy of this signed consent form to keep.

If you're willing to volunteer for this research, please sign the next page.

Subject's Printed Name

Subject's Phone Number

Subject's Signature

Date

Time

Person Obtaining Consent

Date

Time

03-05-02
Revised 04-19-02
Revised 12-27-02
Revised 01-29-03
Revised 03-05-03
Revised 04-02-03
Revised 05-02-03
Revised 07-21-03
Revised 03-16-04

PATIENT INFORMATION & ELIGIBILITY CHECK LIST

NAME: _____ STUDY # _____

PHONE: (h) _____ (w) _____

(cell) _____

_____ 1. AGE ?

_____ 2. HX OF BREAST CANCER ?

_____ 3. FAMILY HISTORY OF BREAST CANCER ? IF YES, LIST BELOW

PRE-MEN

POST-MEN

_____ 4. POSITIVE BRCA GENE ?

_____ 5. BENIGN BREAST BIOPSY WITH A PATH DX.
OF ATYPICAL LOBULAR HYPERPLASIA &/OR
LCIS IN SITU ? IF YES, WHERE & WHEN ?

_____ 6. CHEST XRT FOR LYMPHOMA ?

_____ 7. ANY POSSIBILITY OF PREGNANCY?

_____ 8. IMPLANTS (EXCEPT FOR UNI AUGMENTATION FOR MASTECTOMY)

_____ 9. BREAST SIZE

COMPLETED BY: _____ DATE: ____ -- ____ -- ____ ***

*** AS PER PATIENT INTERVIEW

Dear Ms. _____

Thank you for agreeing to participate in our study evaluating stereoscopic digital mammography compared to standard digital mammography. Enclosed is a copy of the consent form. Please read it and if you wish to continue participation, sign the form and bring it with you to your screening appointment. If you have any questions, please do not hesitate to call Dr. Carl D'Orsi at 404-778-4446. All the mammograms will be done on a state-of-the-art digital mammography unit at the Breast Imaging Center at Emory located at 1365-B Clifton Road, N.E. If you have been scheduled for screening at our other screening center (1525 Clifton Road, N.E.), disregard that appointment.

Once again, many thanks.

Sincerely

Dr. Carl D'Orsi, Director
Breast Imaging Center
The Emory Clinic
1365-B Clifton Road, NE
Atlanta, GA 30322

Letter of Revocation for Research Study: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall.

Dear Dr. D'Orsi:

I want to end my participation in the research study that is named above. In addition to ending my participation I would like to [choose one of the following options]:

Option 1: REVOKE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not participate in the research study, and I revoke my authorization to permit the researchers to collect and use any more information about me. I understand and agree that in certain circumstances the researchers may need to use my information even though I have revoked my authorization, for example, to let me know about any safety concerns, or to make any required reports to governmental regulatory agencies.

Option 2: CONTINUE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not actively participate in the research study any more, but the researchers may continue to collect and use information from my medical record as needed for the research study, but only for the reasons discussed in the consent form that I signed.

I understand that the researchers will respond to this letter by letting me know that they have received it.

Sincerely,

Signature of Study Participant

Date

SDM DATA FORM A1 - STANDARD READING

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

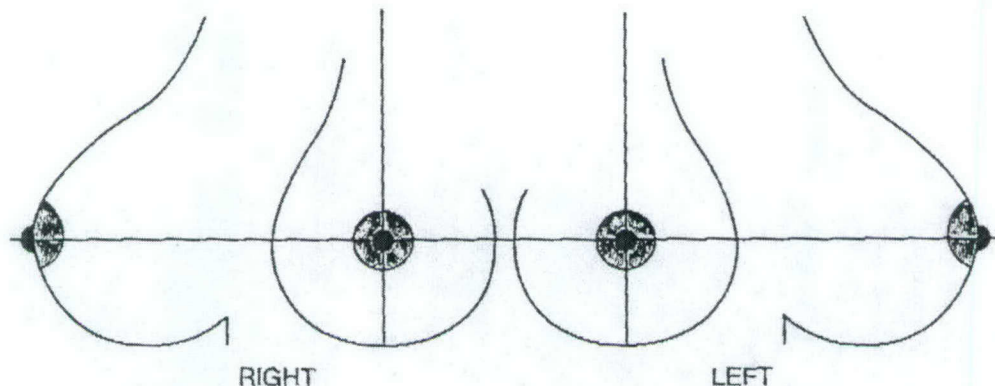
1. Is there a finding(s) which you feel requires recall of the patient?

☐ Yes ☐ No

2. State the number of findings in:

Left Breast	
Right Breast	

3. Mark findings on the picture below using the following codes: M-Mass, F-Focal asymmetry, A-Architectural distortion and C-Calcifications.
(Numbers starting from 1 can be appended to the code for more than one finding of the same type).



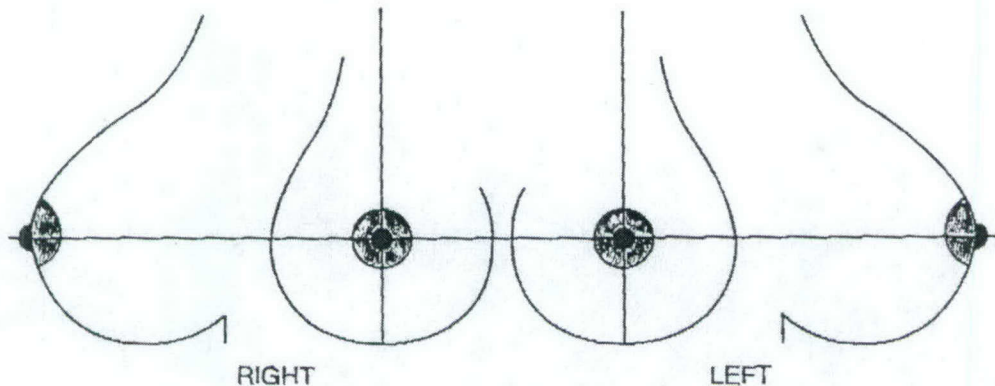
4. Rate the findings:

Finding code	Rate, on a scale of 0 to 100, that the finding is real.	Rate, on a scale of 0 to 100, that the finding is malignant.

READER'S INITIALS: _____

☐ Yes ☐ No

Left Breast	
Right Breast	

[illegible]

SDM Script
18-months Follow-Up Call

Hello Ms. _____

My name is _____ and I am working on the grant you so graciously agreed to participate in about a year and one-half ago when you had a stereoscopic digital mammography exam. We need some information to complete our data for the grant. This should only take about 5 minutes of your time.

Have you had any additional imaging examinations of your breasts, such as ultrasound, MRI or additional mammograms since the stereo digital mammogram?

What recommendations were given to you regarding those exams?

Have you had a breast biopsy or surgery since the stereo digital mammogram?

What were the results?

Thank you for your time. If you have any questions, please call me or Dr. D'Orsi at 404-778-4446.

SDM DATA FORM B
18 MONTHS – FOLLOW-UP CALL

PATIENT STUDY NUMBER: _____

DATE OF CALL: _____

DATE STUDY DONE: _____

1. Other imaging studies since digital mammogram? ☐ Yes (R L) ☐ No
(circle one or both breasts)

Ultrasound	<input type="checkbox"/> Yes (R L)	<input type="checkbox"/> No
Mammogram	<input type="checkbox"/> Yes (R L)	<input type="checkbox"/> No
MRI	<input type="checkbox"/> Yes (R L)	<input type="checkbox"/> No
Other	<input type="checkbox"/> Yes (R L)	<input type="checkbox"/> No

2. If Yes, recommendation resulting from the exam(s):

☐ Normal screening
☐ Accelerated follow-up
☐ Biopsy

3. Breast biopsy since digital mammogram? ☐ Yes (date) _____ ☐ No

If Yes, continue

4. Type of Biopsy: ☐ Excision ☐ Percutaneous
5. Side of Biopsy: ☐ Right ☐ Left ☐ Bilateral
6. Results of Biopsy: ☐ Benign ☐ Malignant
7. If malignant, treatment: ☐ Lumpectomy/Radiation Therapy
☐ Mastectomy
☐ Lumpectomy only
☐ Chemotherapy

SDM DATA FORM C

DISCREPANCY RESOLUTION FORM

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF DISCREPANCY MEETING: _____

READER INITIALS: STANDARD _____ STEREO _____

Finding Codes: M=Mass, F=Focal asymmetry, A=Architectural distortion,
C=Calcifications, ND=Not detected in that reading

<u>Discrepant Finding #1</u>	Original Finding	Reconsidered Finding (for each reading condition)
Standard reading:	_____	_____
Stereo – MLO reading:	_____	_____
Stereo – MLO +CC reading:	_____	_____
Consensus finding:	_____	Confidence (0-100): _____
<u>Reason for discrepancy:</u>		

<u>Discrepant Finding #2</u>	Original Finding	Reconsidered Finding (for each reading condition)
Standard reading:	_____	_____
Stereo – MLO reading:	_____	_____
Stereo – MLO +CC reading:	_____	_____
Consensus finding:	_____	Confidence (0-100): _____
<u>Reason for discrepancy:</u>		

David J. Getty, PhD

Stereoscopic and Biplane Imaging¹

A difficulty with standard projection radiography is that subtle lesions can be obscured by superimposed normal tissue and anatomic structure. Stereoscopic imaging can often resolve this problem by visually separating the superimposed tissue and structure from the lesion in depth, allowing a radiologist to detect the lesion. A second difficulty with projection radiography is that chance superimposition of normal tissue or structure can mimic the appearance of an abnormality, leading to a false-positive detection. Stereoscopic imaging can help to reduce such false-positive findings because the superimposed tissue, now seen as distributed in depth, is much less likely to be perceived as a real lesion. Stereoscopic viewing also has advantages with regard to detected lesions. The location of a lesion in relation to the surrounding tissue and structure can be viewed directly, rather than inferred mentally from multiple planar views. The volumetric shape of a mass or the geometric structure of a cluster of calcifications can also be seen directly.

Many of these advantages of stereoscopic viewing were appreciated early in the development of radiography. Only a few months after the discovery and public disclosure of x rays by Röntgen in 1895, E. Thomson described the acquisition and viewing of stereoscopic x-ray images (1). The medical value of stereoscopic x-ray imaging for localization of tissues and seeing structures in depth was soon appreciated by Sir James Mackenzie Davidson, a prominent British physician who in 1898 published an article on the subject in the *British Medical Journal* (2) and in 1916 published a book containing many illustrative stereoscopic images to demonstrate the utility of stereoscopic x-ray imaging (3).

That so little time passed between the discovery of x rays and the creation of the first stereoscopic x-ray images is not so surprising, given that stereoscopic photography was a popular pastime at the beginning of the past century. It was commonplace for a family to own a parlor version of the Holmes stereoscope (4), an adaptation of an earlier stereoscope developed by Brewster in 1849 (5). Printed stereo cards provided dramatic in-depth views of places and people from around the world.

During the early part of the 20th century, devices were developed to aid the radiologist in viewing a stereo pair of x-ray images. In one type of aid, the x-ray films were mounted side by side on a light box, and a handheld viewing device, which incorporated mirrors (and sometimes lenses) in a metal frame, was held up in front of the x-ray images so that each image was seen by only one eye (Fig 1). This process was awkward, and because it was difficult to align the films precisely, radiologists often experienced some discomfort and eyestrain in using the device. Nevertheless, the added



RSNA'03

value of seeing the imaged tissue and anatomic structures in depth was such that stereo x-ray imaging remained a commonly used technique in radiology departments until the advent of serial section-based x-ray techniques, such as computed tomography (CT) and magnetic resonance (MR) imaging. Over the years, stereoscopic imaging has been applied, to advantage, to many different parts of the human body, including the brain (6), the cranium and face (7,8), the middle ear (9), the larynx (10), the hand and wrist (11), the spine (12-14), the rib cage (15), the pelvis (16), the breast (17,18), and the vascular system (19-21).

In recent years, advances in digital radiography, high-resolution digital display systems, and high-quality stereo viewing devices have made possible the development of medical stereoscopic imaging techniques that avoid the limitations of the earlier film-based methods. A stereo pair of digital x-ray images can be acquired easily and displayed to the radiologist in a way that ensures precise image registration and provides superb perception of depth in the imaged volume without visual strain. Furthermore, the digital display permits the radiologist to control and manipulate several viewed aspects of the stereo image (eg, gray-scale window level and window width, inversion of gray scale, and inversion of depth) that can greatly enhance the value of the stereo imaging.

STEREOSCOPIC VISION

Before a discussion of how stereoscopic medical images are acquired and displayed, it is helpful to review stereoscopic vision briefly. Our visual system provides us with a strong sense of where objects that we see before us are located in depth, relative to one another. In everyday life, the sense of depth receives contributions from many visual cues. Most of these cues are monocular, requiring only one eye to deliver the information. Examples of such cues are the relative retinal size of familiar objects, interposition and occlusion of objects, linear perspective, aerial perspective (increasing blueness and blurring of objects with growing distance), highlights and shading from light sources, and movement parallax (22). Although these monocular cues are important to us in perceiving and navigating the world around us, they are of little or no value in discerning the relative depth of structures in medical x-ray images. However, one other potent depth cue, stereopsis ("solid seeing"), uses and requires input from both eyes to provide us with depth information. This cue has the potential to provide depth information in medical images acquired as stereo pairs.

Because our two eyes are separated by about 65 mm horizontally, each has a slightly different view of the world. You can easily demonstrate this difference to yourself by holding up one finger, looking at it first

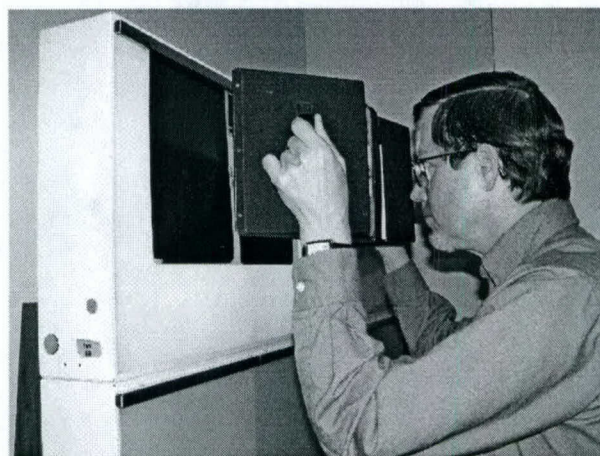


Figure 1. Demonstration of a handheld device made many years ago for viewing a stereo pair of standard radiographs mounted side by side on a view box. The device uses two pairs of angled front-surface mirrors to redirect the image from each film to the appropriate eye while permitting the observer to look straight ahead.

with one eye (while closing the other) and then with the other. You will notice that the position of objects in the background, relative to the position of your finger, changes in the images seen by your two eyes. The basis of stereopsis is the angular horizontal disparity between corresponding points of an object in the two retinal images. When you fixate an object, your eyes rotate, or "converge," to bring the point of fixation onto the fovea of each retina. There is zero retinal disparity in the depth "plane" defined by the point of fixation. A point on an object that lies farther away from you than the fixation point creates images on the two retinas that have "positive" retinal disparity, determined by the angular difference of the corresponding points from the fovea on the two retinas. Similarly, points on an object that lies closer to you than the fixation point create retinal images that have "negative" retinal disparity. The magnitude and sign of the retinal disparity are sufficient to determine the depth of an object relative to the point of fixation.

The visual system has evolved to take advantage of the relative depth information contained in the retinal disparity present in the retinal images of the left and right eyes. Within the visual cortex, input from the two views is fused into a single perceived view in which we see objects in depth. Julesz (23) has referred to this unitary perception as the "cyclopean eye." He and others have developed models of how networks of binocularly driven cells in the visual cortex may cross-correlate the images from the two eyes, with different layers of topographically organized cells detecting different amounts of horizontal shift. A high correlation at a particular location in a particular layer would correspond to detection of an object in the visual field at a particular location and a particular depth.

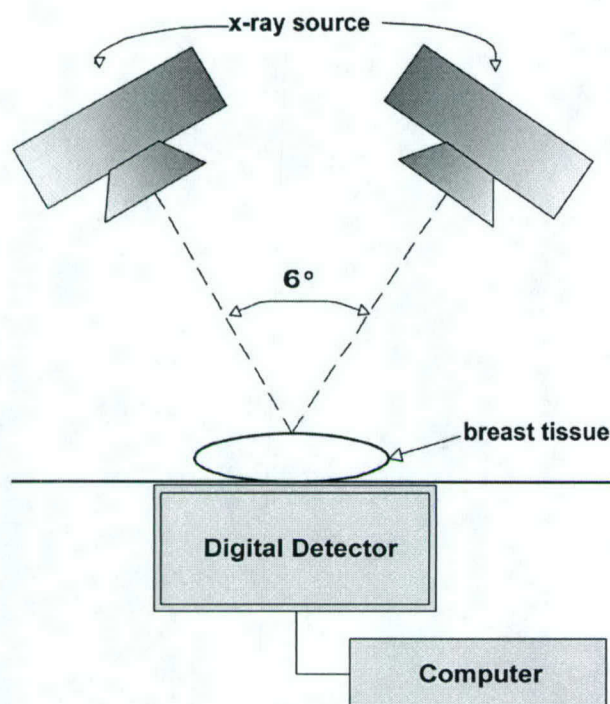


Figure 2. Acquisition of a stereo pair of digital mammograms. The x-ray source is initially rotated 3° away from the perpendicular to the digital detector surface. After one exposure, the source is then rotated by 6° (3° from the perpendicular in the other direction) before the second exposure. The detector and the tissue being imaged remain fixed in position while the source is rotated.

ACQUISITION OF STEREO IMAGE PAIRS

In a famous paper presented in 1838, Wheatstone (24) observed that one can create the perception of depth in an artificial visual scene by presenting separately to each eye a planar image corresponding to what would be seen by that eye as it observed that scene. He demonstrated his insight by creating a number of drawings of objects distributed in depth, as would be seen by the left and right eyes, and displayed them in a mirror-based stereoscope that he invented.

Photography was developing during that same era, and it was not long before Wheatstone's device was being used to view stereo pairs of photographs. To capture a stereo pair, one takes two photographs of a scene, separated by a horizontal shift of the camera of about 65 mm, corresponding to the average distance between the eyes (25). When viewed in a stereoscope that directs each image solely to the appropriate eye, the two images are fused in the mind's cyclopean eye into a single image perceived in depth, as if one were standing where the camera had been.

The same principle applies to the acquisition of stereo pairs of x-ray images. Two sequential x-ray exposures are made of the object to be imaged, with the x-ray source shifted by a small angular amount be-

tween the two exposures, as shown in Figure 2. There are, however, several important considerations in acquiring the stereo pair.

Fixed Object

It is critical that the object being imaged not move or deform in any way between the two x-ray exposures. Any such movement or deformation will result in two images that (a) create considerable visual strain and discomfort for the viewer when the visual system attempts to fuse the two into a single in-depth image or (b) simply cannot be fused. This requirement also implies that the table holding the object to be imaged must be fixed, independent of the movement of the x-ray source.

Independence of the Detector and the X-ray Source

Ideally, the x-ray detector, located beneath or behind the object to be imaged, should also remain fixed, in an unchanging relationship to the object being imaged, as the x-ray source is moved between the two exposures. In most systems, the x-ray source is mounted on a gantry such that its movement is achieved by rotation about an axis. The stereo pair of images is acquired by rotating the x-ray source by a small angle to either side of the perpendicular to the detector, as shown in Figure 2.

A problem arises, however, if the x-ray source and detector are yoked together so that both rotate together, as in some mammography systems. The resulting pair of images will suffer from keystone distortion, as shown in Figure 3. There will be noncorresponding vertical magnification in the two images that is greatest near the left and right edges. This magnification will make it difficult or impossible for a viewer to fuse the pair into a single stereo image because the visual system is intolerant of vertical disparity, which does not occur in normal vision. The situation can be remedied, however. It is possible to apply a mathematical transformation to each digital image to undo the keystone distortion—in effect, to project each image back to a fixed, correct plane. The transformation may result in a small, but probably tolerable, amount of pixel quantization error.

Angle of Separation

How much of an angular separation should one use between the two exposures in acquiring a stereo pair of x-ray images? The larger the angular separation, the greater will be the perceived depth. However, most people experience increasing visual strain when attempting to view stereo image pairs that are acquired with more than about 8° or 9° of angular separation. Thus, the angle of separation between the two images should in most cases not exceed this limit. In our own work, we have found a separation of 6° to be a good

compromise. Another issue that bears on the angle of separation and conditions for viewing the stereo image will be discussed subsequently in this chapter (see "Location of the Observer Relative to the Display Screen" section).

STEREOSCOPIC DISPLAY SYSTEMS

The goal in displaying a stereo image pair is to channel the image intended for the left eye solely to the left eye and the image intended for the right eye solely to the right eye while maintaining precise alignment of the two images. A number of methods have been developed to accomplish this goal, and they can be categorized in several ways (26). A major distinction is whether or not the observer has to wear special glasses or other headgear. Most systems, referred to simply as *stereoscopic display systems*, do require the observer to wear glasses or other gear. Other systems, referred to as *autostereoscopic display systems*, permit the observer to view the stereo image freely, without encumbrance. Both types of system are discussed in the subsequent paragraphs, with the discussion restricted to systems appropriate for the display of stereo digital radiographs.

Autostereoscopic Display Systems

Current autostereoscopic display systems that are capable of displaying medical stereo image pairs are based on "parallax barrier" techniques. The left- and right-eye images are interleaved on the display, typically a liquid crystal display (LCD), such that successive columns of pixels alternate between left- and right-eye images. In some systems, a grid plate with a series of vertical slits, at half the frequency of the pixels, is placed in front of the LCD elements. When the observer is seated directly in front of the display at a specified distance, the solid vertical strips of the grid block the right eye's view of the left-eye pixel columns and, similarly, the left eye's view of the right-eye pixel columns. In other systems, the grid is located between the illumination source and the matrix of LCD elements, creating a series of vertical light strips. Some systems have used a lenticular lens sheet placed over the LCD matrix. The sheet consists of a horizontal series of vertically oriented cylindrical lenses, each the width of two pixel columns. The lenses bend light from the left-eye columns of the LCD slightly to the left and light from the right-eye columns slightly to the right.

One major limitation of these systems is the restriction of the viewer to a particular location in front of the display. Several groups have recently worked on adding eye tracking to the display system, for example, by using two video cameras mounted on top of the display to dynamically determine the observer's current eye location and to dynamically adjust the parallax grid to channel the alternating pixel columns to the appropriate eye. If this enhancement proves effective,

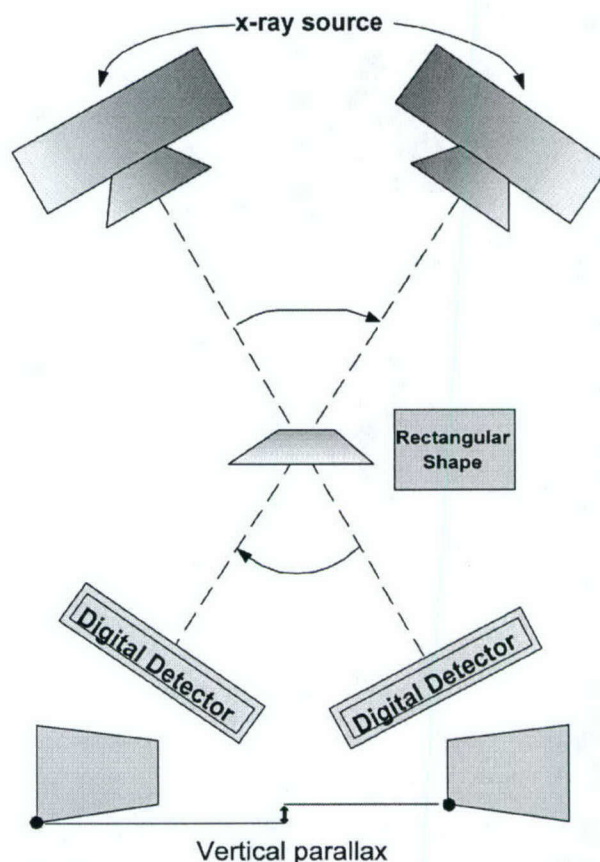


Figure 3. Linked rotation of the x-ray source and of the digital detector that results in keystone distortion in the acquired stereo pair of images. As shown, exposure of a rectangular object would result in trapezoidal images in which corresponding points in the two images would be displaced vertically, particularly near the left and right edges.

it would allow the viewer some degree of freedom to move in front of the display while maintaining a stereo image.

A second limitation of this type of display is the limited horizontal resolution. Because left- and right-eye columns of pixels alternate on the display, the horizontal pixel count is only half that of the display, with no similar reduction vertically.

Stereoscopic Display Systems

Spatially multiplexed systems.—Systems in which both left- and right-eye images are simultaneously conveyed to each eye through spatially separate channels are said to be *spatially multiplexed*. All of the mechanical stereoscopes described earlier are of this type. The simplest spatially multiplexed digital systems divide the display screen in half, with each image of the stereo pair occupying only half of the screen. A device that is held, or attaches to the front of the monitor, contains mirrors and optics that deliver each image to the appropriate eye. The obvious limitation is that horizontal pixel count is limited to half of the screen width.

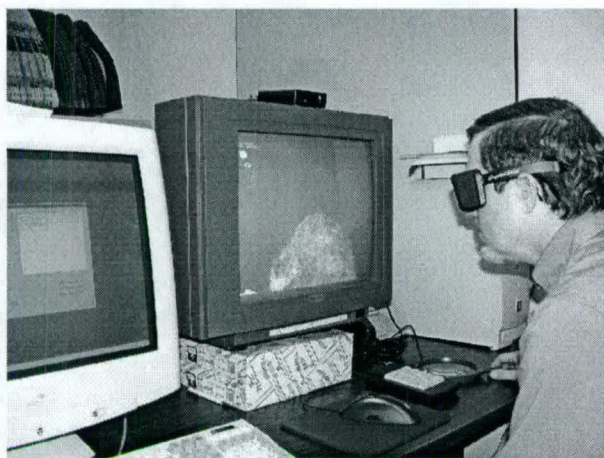


Figure 4. Example of a temporally multiplexed stereoscopic display workstation. The two stereo images are presented alternately on the high-resolution monitor at a 120-Hz frame refresh rate. The small black box on top of the monitor emits an infrared synchronization signal. This signal is picked up by the special glasses worn by the observer and triggers LCD optical shutters in the two lenses to open and close in opposition, routing each image to the correct eye.

Other systems use two separate display monitors, each dedicated to just one of the images. Various devices have been devised to deliver the image of each monitor to the appropriate eye. This technique is rarely used because of the large amount of equipment involved and the difficulty of matching the two monitors and aligning the two display images precisely enough. The continuing development of miniature high-resolution displays may eventually lead to a small lightweight piece of headgear containing two small monitors that deliver a stereo image.

Temporally multiplexed systems.—By far the most common method of displaying stereo digital image pairs makes use of *temporal multiplexing*. In this case, both left- and right-eye images are displayed on a single monitor, with the two images alternately presented on successive frames. The trick, of course, is to find a way to deliver each image to the appropriate eye—and only to that eye. Current systems use special glasses equipped with LCD lenses that act as optical shutters. One such system is shown in Figure 4. Each lens can be made either clear (effectively, two layers of polarization in the same direction) or opaque (two layers of polarization at right angles). At the beginning of each successive frame, the glasses receive an infrared synchronization signal from the display controller card that enables the glasses to track when each image is being displayed on the monitor. When the left-eye image is being displayed, the left-eye lens of the glasses is clear, and the right-eye lens is opaque. On the next display frame, when the right-eye image is being displayed, the optical shutters of both lenses switch state, and so on continuously. Note that each eye is seeing only every other frame. To avoid perceived flicker of the image, the

monitor must be driven at a high refresh rate, typically on the order of 120 Hz. Thus, each eye sees an image refreshed at 60 Hz, a rate high enough to avoid flicker in most circumstances.

In a related type of system, the optical shutter is a large LCD sheet that covers the entire front surface of the monitor. The observer wears lightweight, passive polarized glasses with the axis of polarization 90° apart in the two lenses. The polarization of light passing through the LCD sheet matches that of one lens on one display frame and is rotated by 90° to match the other lens on the next display frame. The advantage of this method is the lighter weight of the glasses. A disadvantage is that the large LCD sheet is more prone to damage and, in general, must be left on the monitor all of the time.

With either method, the luminance of the image seen by the observer is reduced to about 32% of the luminance of the image present at the face of the monitor because of losses of light with passage through the LCD lens (and polarized glasses in the second technique). Thus, the brightness of the image is reduced considerably compared with a nonstereo soft-copy display.

A potential artifact with this method of display is ghosting. If the phosphor used in the monitor is relatively slow to decay after being activated on one display frame by the scanning electron beam, then an image presented, say, to the left eye may not have disappeared entirely at the start of the next frame when the right-eye lens is open. Each eye may therefore see a faint ghost of the image from the preceding frame, intended for the other eye.

This ghosting can reduce considerably the effectiveness of the stereo presentation and the amount of depth perceived in the image. Thus, there is a need to choose a phosphor for the monitor that exhibits rapid decay. One might imagine that substituting a flat-panel LCD for the cathode ray tube monitor would solve the problem. However, current LCD monitors also exhibit persistence caused by electronics and liquid crystal memory effect that can be as long as 25–50 msec. If high frame rates are used to avoid flicker, ghosting would occur because of the long pixel transition times. A second problem with current LCD monitors is that the transmitted light is polarized. This polarization will typically be in a plane that conflicts with the polarization plane of the stereo LCD glasses, and if not taken into account, it can reduce the luminance of the display.

A high-resolution, gray-scale stereo display workstation of this type has recently been developed (Fig 4). This device is capable of displaying an entire digital mammogram ($2,304 \times 1,800$ pixels) at once in stereo, at a 120-Hz refresh rate. The observer wears stereo LCD glasses that are synchronized to the display by an infrared emitter. Because of the high pixel density on the display, the observer is even able to use a magnifying

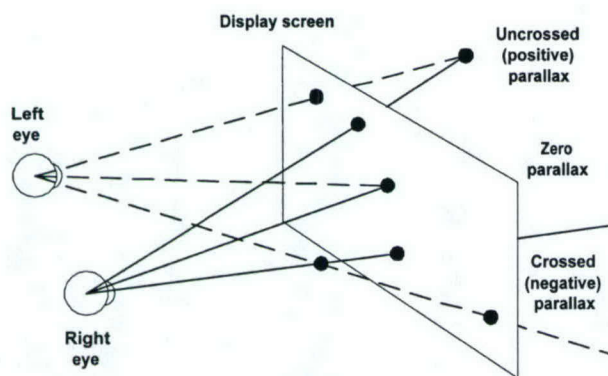


Figure 5. Illustration of uncrossed (positive), zero, and crossed (negative) parallax of pairs of corresponding points shown on a display screen. In a temporally multiplexed display, only the points intended for the right eye (solid lines) or those for the left eye (dashed lines) would be visible on the screen at one time. These points are shown together here to illustrate the perceptual effects of different types of horizontal displacement.

glass on the stereo image to observe detail, seen in depth, at greater magnification.

DISPLAY OF THE STEREO IMAGE

Horizontal Parallax

In a stereo display, the retinal disparity that leads one to perceive depth in natural vision is created by horizontal parallax—the horizontal separation of corresponding points in the left- and right-eye images on the display screen (27). There are three types of parallax, as illustrated in Figure 5. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have “zero parallax.” The perceptual effect is that the object is seen to lie at the surface of the display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye images. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called “uncrossed” or “positive” parallax.

In the third case, if the right-eye point is displaced to the left of the left-eye point, which is called “crossed” or “negative” parallax, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface, toward the observer.

Depth Quantization

Because we are working with digital images, the amount of horizontal parallax between pairs of corresponding points in the two images is necessarily an integer multiple of the spacing between pixels. Consequently, the perceived location of points in depth will

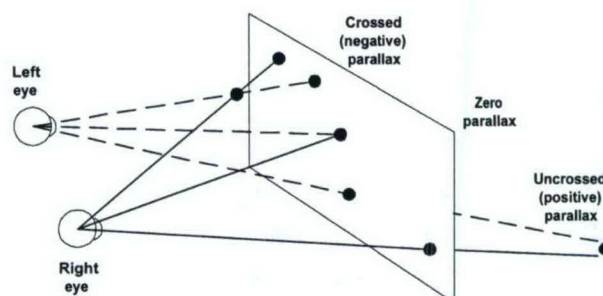


Figure 6. Inversion of perceived depth achieved by swapping the two images. Points that had been seen by the right eye in Figure 5 are now seen by the left eye (now shown with dashed lines), and points that had been seen by the left eye are now seen by the right eye (now shown with solid lines). By comparing this figure with Figure 5, one can see that depth has been inverted: points that showed uncrossed parallax in Figure 5 now exhibit crossed parallax, and those that showed crossed parallax now exhibit uncrossed parallax. Points with zero parallax remain unchanged.

also occur in quantized depth planes. The actual functional relationship between pixel spacing and depth plane spacing also depends on the distance of the observer from the display screen, as will be discussed subsequently (see “Location of the Observer Relative to the Display Screen” section).

Manipulations of the Stereo Image

Inversion of depth.—Although the stereo point of view of the imaged object is predetermined by the point of view at the time of image acquisition, the observer can manipulate two other aspects of the viewed volume (27). First, one can invert depth by swapping the two images—presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Figure 5. When we swap the images, as shown in Figure 6, the dot previously seen by the left eye is now seen by the right eye, and vice versa. So now we have crossed parallax, and the object will be seen not behind the screen but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa. Dots with zero parallax will still have zero parallax and continue to be seen at the screen surface. Thus, the effect of swapping images is to invert depth—much like reaching into a glove and pulling it inside out. If, in addition to swapping the two images, one also spins each image 180° about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the back.

Inverting depth can be important in stereo viewing, especially of mammograms. It is easier to attend to objects seen in the foreground than those seen in the background, especially when there is a clutter of objects in the foreground. When a radiologist is allowed

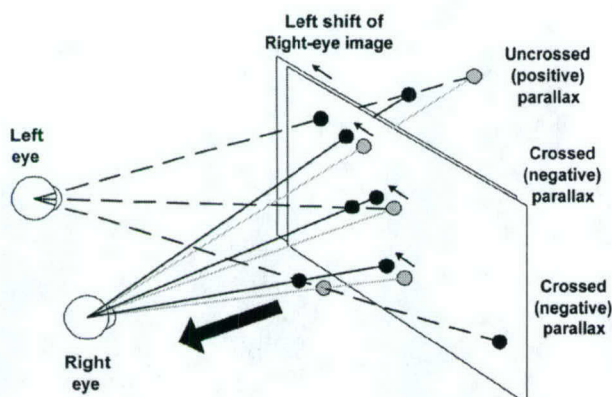


Figure 7. Shifting of the displayed volume either toward or away from the observer through horizontal shifts of one or both images relative to the other. This figure illustrates a leftward shift of the right-eye image relative to the left-eye image, which causes the entire displayed volume to shift toward the observer. A rightward relative shift of the right-eye image relative to the left-eye image would cause the displayed volume to move away from the observer.

to invert depth, tissue originally at the back of the displayed volume can be moved to the front of the volume, making the tissue easier to perceive and inspect.

Shifting location of the viewed volume.—A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Figure 7, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, toward the observer, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image or to both images. In fact, splitting a desired amount of shift between the two images will minimize the amount of stereo image lost at the left and right edges of the display.

Control of location of the viewed volume is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes toward them in space. They are usually more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It is always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often come to prefer a

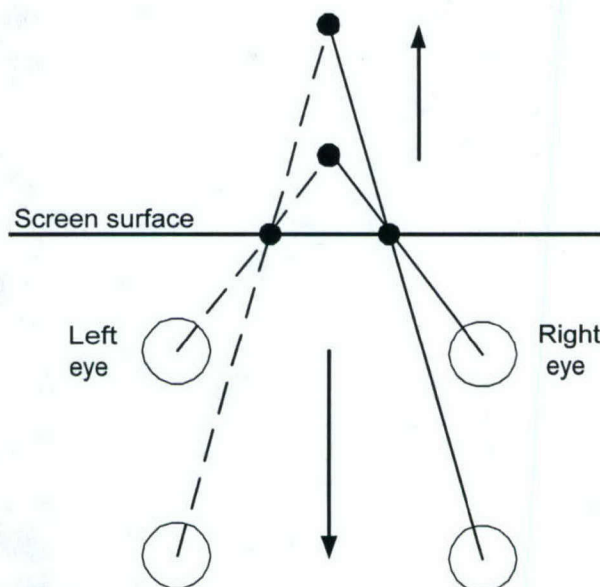


Figure 8. Relationship between distance of the observer from the display screen surface and perceived depth of a point displayed with fixed horizontal parallax between the left- and right-eye images. Increasing observer distance from the display screen results in greater perceived depth in the stereo image.

displayed volume that comes out into space. As an interesting note, when the stereo image is occupying accessible physical space in front of the screen, one can actually use a finger or pencil to point out to other observers an object of interest within the volume.

PERCEPTUAL CHARACTERISTICS OF THE STEREO IMAGE

Location of the Observer Relative to the Display Screen

Does it matter how close or far away the observer is from the display screen? In part, the answer is "yes." In Figure 8, two corresponding points, one intended for the left eye and the other for the right eye, are shown with uncrossed parallax, resulting in perception of a point located behind the display screen. If the observer moves back from the closer viewing position to the more distant one, the location of the perceived point moves further back in depth. The two distances are directly proportional to one another. Thus, as the observer moves away from the display screen, the amount of perceived depth in the displayed stereo image will increase.

Is there a "correct" distance, then, for the observer to be from the screen? If the observer wants the amount of perceived depth to be the same as the actual depth that was present in the imaged object, then the answer is again "yes." As shown in Figure 9, the observer wants to be at a distance from the screen such that the angle, α , formed between the observer's two eyes and

a central point on the screen, is equal to the separation angle used in acquiring the stereo image pair. For an acquisition separation angle of 6° , the appropriate viewing distance is about 62 cm (about 24 inches). If the observer is farther away than this distance, perceived depth will be greater than the actual depth of the object; if the observer is closer, then perceived depth will be less than actual depth. The relationship is given by the following formula: correct viewing distance = $3.25 \text{ cm} / \tan(\text{acquisition angle}/2)$, where 3.25 cm represents half of the average interocular spacing of 6.5 cm. The smaller the separation angle at acquisition, the larger the correct viewing distance. In practical terms, one's perception of this change in depth with viewing distance is small for the range of distances that a radiologist finds comfortable and useful and is therefore not of much consequence.

Because corresponding points in the two images of a stereo pair bear a fixed relationship to one another—determined at the time of image acquisition—sideways movement of the observer causes the viewed stereo image to appear to rotate, so as always to present exactly the same point of view to the observer. Because the two images are fixed, the observer cannot alter his or her point of view of the object by moving from side to side. Also, the observer should not tilt his or her head while viewing the stereo image. Head tilt will cause corresponding points in the two images to be displaced from one another vertically on the two retinas, making it increasingly difficult to fuse the two images with increasing tilt.

Depth Acuity

Our ability to discriminate the relative depth of objects in normal vision—to say which is nearer, for example—is remarkably good. Depth acuity is usually measured in terms of the difference in angle two objects at different depths create at the two eyes. Studies have shown that when the objects are vertical line segments, we can detect a difference in depth corresponding to as little as 2–6 seconds of arc (28).

Some studies of depth acuity have been conducted for accuracy of placement of a cross-hair cursor in depth in digital stereo mammograms. Goodsitt et al (29,30) acquired a stereo x-ray image of a phantom containing low-density fibrils with both vertical and horizontal orientations, at depths ranging from 1 to 11 mm. The observer's task was to move a cursor to the depth of each fibril while viewing the stereo image. They found that observers were able to place the cursor accurately for vertical fibrils, with standard errors ranging from 0.39 to 1.33 mm across observers. Accuracy of placement for horizontal fibrils was substantially worse, however, with standard errors ranging from 1.87 to 4.19 mm.

This difference can be understood in terms of the information provided to the visual system. For the verti-

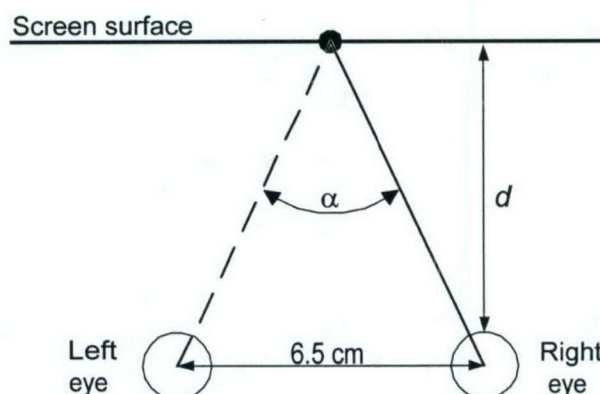


Figure 9. Illustration of the variables that determine the "correct" viewing distance by the observer, in which perceived depth is the same as the actual depth within the imaged object.

cal fibrils, every point along the length of the fibril contributes corresponding points on the two retinas that exhibit horizontal disparity. The longer the fibril, the more points there are to contribute depth information. On the other hand, for the horizontal fibrils, the only truly identifiable points that will produce horizontal disparity are the two ends of the fibril. For intermediate points, the visual system will have a hard time identifying corresponding points in the two retinal images because they are indistinguishable. The implication is that a radiologist will be much better at determining the depth of objects in stereo radiographs that have a lot of vertical structure and will be less able to determine the depth of objects that have predominantly horizontal structure. This also means that if one constructs a three-dimensional cursor that can be moved in depth, it should have strong vertical components.

AN APPLICATION OF STEREO IMAGING: STEREOSCOPIC DIGITAL MAMMOGRAPHY

A preliminary project has recently been completed to evaluate the contribution of stereo mammography in the diagnosis of breast cancer (17). During a period of several years, we acquired both standard film and stereo digital mammographic images of the breasts of a number of women scheduled for biopsy of a suspicious focal breast lesion. The stereo mammograms were acquired with a preclinical version of a digital mammography unit, with a 6° shift in the x-ray tube between exposures while the detector and breast remain fixed in position. An illustrative stereo pair of digital mammograms is shown in Figure 10. We conducted a reading study to determine the diagnostic accuracy achieved with standard film alone compared to the diagnostic accuracy achieved with standard film read together with the stereo mammogram. A second goal, which was added as the project progressed, was to obtain preliminary data on the capability of stereo



Figure 10. Stereo pair of digital mammograms acquired on a preclinical version of a digital mammography unit. The x-ray source was rotated by 6° between the two exposures ($\pm 3^\circ$ either side of the perpendicular to the detector surface). Although the two images look similar, different amounts of horizontal parallax are present for corresponding points at different depths in the imaged breast tissue. It is possible to experience the fused stereo image by crossing one's eyes. A benign mass is seen on the mammogram at 8 o'clock. When viewed in stereo, the location and orientation in depth of the many strands of fibrous tissue and vessels become readily apparent.

mammography to depict subtle lesions that are not visible on the corresponding standard films.

The reading study was conducted with five experienced mammographers individually reading the images from 129 pathologically proved cases with 137 malignant and benign lesions (several patients had more than one lesion). The reading of each patient's images was conducted in two successive stages. The reader first examined the full set of film mammograms from the diagnostic study that led to biopsy, rating the probability that the lesion was malignant on a scale of 0–100. The reader was then shown the stereo view of the lesion and asked to rate the probability of malignancy again. The stereo images were viewed on a stereo display workstation capable of displaying the entire digital mammogram ($2,304 \times 1,800$ pixels) at half resolution or a $1,024 \times 512$ region of interest centered around the lesion at full resolution. The stereo image was always a craniocaudal view acquired just before biopsy. For each case, the reader was also asked to report any additional lesions seen in either the films or the stereo mammogram, in addition to the known lesion subjected to biopsy.

We conducted a receiver operating characteristic-based analysis of the accuracy of the readers' ratings of the likelihood of malignancy for the two viewing conditions. Diagnostic accuracy, which was measured with A_z (area under the receiver operating characteristic curve), was 0.83 when readers viewed the films alone and increased to 0.86 when they also viewed the stereo mammogram, a statistically significant improvement ($P < .01$).

Perhaps a more important finding was that readers detected a considerable number of likely new lesions with the stereo mammograms, lesions that were not detected in the films. In all, 39 new lesions were reported in the 129 cases, corresponding to 30% of the cases. Of these 39 lesions, 30 were reported as masses,

six as new calcification clusters, and three as architectural distortions. Although we do not have independent truth for many of these newly detected lesions, we do have truth for one subset: masses detected only in the stereo mammogram in association with prior film-detected calcifications. For 11 of 12 such cases, the pathology report stated that the calcifications were located within a mass (most often a fibroadenoma).

As a follow-up, we are now beginning a large clinical study of stereoscopic digital mammography, funded by the US Army's Breast Cancer Research Program. In this study, 2,000 women at high risk for development of breast cancer will undergo digital screening mammography, including stereo imaging. We will compare independent readings of the images from each case performed by different mammographers with stereo and standard nonstereo reading conditions. The hypothesis is that stereo imaging will lead to earlier detection of small subtle lesions and, by increasing the confidence of the reader, to a reduced rate of recall of patients for further work-up.

DOUBLE THE X-RAY DOSE WITH STEREO IMAGING?

On the face of it, it would seem that the total x-ray dose to acquire a stereo pair of digital radiographs would be twice the dose of a single nonstereo digital radiograph. Each image in a stereo pair, however, represents an independent sampling of x-ray quantum mottle. When the visual system of the observer fuses the two images into a single cyclopean perception, it is possible that quantum noise in the fused image will be reduced compared with that of a single nonstereo radiograph. In fact, signal detection theory suggests that the signal-to-noise ratio of the fused image may be increased by the square root of 2 because of the independence of the quantum noise in the two images.

The theory suggests that the x-ray dose per image might be reduced by half while still maintaining the same level of detectability as the single nonstereo radiograph.

Maidment (31) and his colleagues have performed several contrast-detail studies using digital images of a mammographic phantom acquired at different exposures to test this hypothesis. Five observers viewed these images on a monitor while wearing stereo LCD glasses. For the nonstereo reading condition, the same image was presented to both eyes; for the stereo reading condition, a stereo pair of images was viewed stereoscopically. Of importance, the stereo pair was acquired with no angular separation between the two exposures, so that no depth was seen when the pair was viewed stereoscopically. This was done to remove the possibly confounding effect that depth would have introduced into the detection of details. Maidment (31) wished to test only the effect of independent samples of quantum noise seen by each eye on the ability to detect details in the images.

One result was that, for a fixed x-ray exposure level, more details were seen in the stereo images than in the nonstereo images, as predicted by signal detection theory. A second conclusion was that the total dose needed to produce a stereo pair of images with detectability of details equal to that of a single nonstereo image was only 1.1 times the dose used for the nonstereo image. Thus, it may be that, depending on the signal-to-noise ratio needed for a particular diagnostic task, the total x-ray dose for a stereo radiographic pair of images may not need to exceed that of a single nonstereo image by much. Of course, this is not taking into account the considerable benefit that may be provided by seeing the imaged object in depth.

BIPLANE CORRELATION IMAGING

Stereo pairs of x-ray images have been used for other things besides in-depth visualization of human organs. For example, stereo pairs of digital mammograms, acquired with a separation angle of 30° , have been used for some time in stereotactic biopsy systems. The large separation angle permits precise localization of an abnormality in the breast tissue, enabling placement of a guide wire into the abnormality. In this case, however, the radiologist does not ever view the two images stereoscopically and, in fact, would be unable to fuse the two images because of the large separation angle. Instead, the radiologist identifies the location of the abnormality in each of the two planar images, and a computer determines the three-dimensional coordinates of the abnormality from those two locations.

Samei et al (32) have recently proposed another nonstereoscopic use for stereo pairs of x-ray images. In recent years, a number of systems have been devel-

oped for computer-aided detection (CAD) of abnormalities in the breast and the lungs as a means of aiding radiologists in the detection of subtle abnormalities. A limitation of these systems is that they often identify a considerable number of false-positive lesions because of superimposed normal anatomic structures. These false-positive findings require individual examination and rejection by the radiologist. These investigators (32) reasoned that the false-positive rate could be reduced if one acquired a stereo pair of images separated by a small angle and then cross-correlated the detections for each of the two images. Only those candidate lesions seen in the same area in both images would likely be true positives. Other candidate lesions seen in only one image would most likely be the result of chance superposition seen from that particular point of view and could be rejected.

Samei et al (32) acquired pairs of digital posteroanterior and oblique radiographs of the lung, separated by varying angles. They applied CAD processing to each image to detect subtle lung lesions and then eliminated likely false-positive findings by applying a cross-correlation rule between the two views. They found that 3° of separation between the two views was optimal and that although detection sensitivity was reduced by about 20% from single-view CAD, the false-positive rate per image was about 94% less than that of single-view CAD. The relative improvement in false-positive reduction was higher for smaller nodules. The positive predictive value improved by 140%. Thus, the use of biplanar views in CAD dramatically reduced the false-positive rate and improved the positive predictive value.

In conclusion, we have witnessed the rapid emergence of digital radiographic techniques in recent years. We have also seen the equally important companion development of high-resolution, high-performance digital soft-copy displays. The combination has led to renewed interest in stereoscopic viewing of radiologic images, with application in many areas of radiology.

As one example, in the past several years, important advances have been made in the quality and speed of software applications that provide volume renderings of volumetric data sets, such as those captured by CT and MR imaging (33). In the past, this type of image processing was performed on separate specialized workstations. Now, many equipment manufacturers are beginning to incorporate this capability directly into the viewing stations attached to the imagers. Currently, an observer senses the volumetric shape of rendered surfaces through monocular visual cues such as shading and highlighting of the surface and through dynamic rotation of the point of view. Stereo imaging offers a potentially useful extension to this capability. To see a rendered volume as a stereo image in depth, the software need only compute images seen from two points of view, separated horizontally by about 6° , and present these two images on a stereo display work-

station. With sufficient computing power, the observer could fly the general point of view around in the imaged volume, providing a "magic carpet" tour of the rendered surfaces.

Stereoscopic image acquisition and display should be relatively easy and inexpensive to implement in the newly emerging digital radiographic systems. For example, there is currently considerable research interest in tomosynthesis of the breast. The modifications of the digital mammography unit needed for tomosynthesis are exactly those needed for stereo image acquisition, namely, an ability to move the x-ray source automatically through a succession of small angular offsets, obtaining an exposure after each movement.

A number of medical research groups are now pursuing research on stereoscopic imaging in radiology. We may expect interesting progress from them in the next several years.

References

- Thomson E. Stereoscopic Röntgen pictures. *Electrical Engineer* 1896; 21:256.
- Davidson JM. Remarks on the value of stereoscopic photography and skiagraphy: records of clinical and pathological appearances. *Br Med J* 1898; 1979:1669-1671.
- Davidson JM. Localization by x rays and stereoscopy. London, England: HK Lewis, 1916.
- Holmes OW. History of the "American stereoscope." *Philadelphia Photographer*, 1869; 6:1-3.
- Brewster SD. An account of a new stereoscope. In: *Proceedings of the 19th Meeting of the British Association for the Advancement of Science*. London: British Association for the Advancement of Science, 1850.
- Graf von Keyserlingk D, De Bleser R, Poeck K. Stereographic reconstruction of human brain CT series. *Acta Anat (Basel)* 1983; 115:336-344.
- Abbott AH, Netherway DJ, David DJ, Brown T. Craniofacial osseous landmark determination from stereo computer tomography reconstructions. *Ann Acad Med Singapore* 1990; 19:595-604.
- Rothman SL, Allen WE III, Kier EL. Stereo roentgenography in craniofacial injuries: a revival of fundamental ideas. *Radiol Clin North Am* 1973; 11:683-696.
- Greenwell FP. Stereo-radiography of the middle ear. *Br J Radiol* 1973; 46:159.
- Sakakura A, Yamamoto Y, Uesugi Y, et al. Stereoscopic display of a three-dimensional image of the larynx using high-speed helical scanning. *ORL J Otorhinolaryngol Relat Spec* 2000; 62:290-295.
- Runciman RJ, Bryant JT, Small CF, Fujita N, Cooke TD. Stereoradiogrammetric technique for estimating alignment of the joints in the hand and wrist. *J Biomed Eng* 1993; 15: 99-105.
- Andre B, Dansereau J, Labelle H. Optimized vertical stereo base radiographic setup for the clinical three-dimensional reconstruction of the human spine. *J Biomech* 1994; 27: 1023-1035.
- Pearcy MJ. Stereo radiography of lumbar spine motion. *Acta Orthop Scand Suppl* 1985; 212:1-45.
- Stokes IA, Bigalow LC, Moreland MS. Three-dimensional spinal curvature in idiopathic scoliosis. *J Orthop Res* 1987; 5: 102-113.
- Dansereau J, Stokes IA. Measurements of the three-dimensional shape of the rib cage. *J Biomech* 1988; 21:893-901.
- Gautsch TL, Johnson EE, Seeger LL. True three dimensional stereographic display of 3D reconstructed CT scans of the pelvis and acetabulum. *Clin Orthop*, August 1994; 138-151.
- Getty DJ, Pickett RM, D'Orsi CJ. Stereoscopic digital mammography: improving detection and diagnosis of breast cancer. In: *Computer assisted radiology and surgery (CARS-2001)*. Berlin, Germany: Elsevier Science, 2001; 506-511.
- Hsu J, Chalberg D, Babbs C, Pizlo Z, Delp E. Preclinical ROC studies of digital stereomammography. *IEEE Trans Med Imaging* 1995; 14:318-327.
- Doi K, Duda EE. Detectability of depth information by use of magnification stereoscopic technique in cerebral angiography. *Radiology* 1983; 146:91-95.
- Doi K, Patronas NJ, Duda EE, Geldner E, Dietz K. X-ray imaging of blood vessels to the brain by use of magnification stereoscopic technique. *Adv Neurol* 1981; 30: 175-189.
- Sekiguchi R, Satake M, Oyama H, Wakao F, Moriyama N. Stereoscopic visualization system for clinical angiography. *Stud Health Technol Inform* 1996; 29:690-693.
- Hochberg JE. *Perception*. Englewood Cliffs, NJ: Prentice-Hall, 1978.
- Julesz B. *Foundations of cyclopean perception*. Chicago, Ill: University of Chicago Press, 1971.
- Wheatstone C. Contributions to the physiology of vision. Part the first. On some remarkable, and hitherto unobserved phenomena of binocular vision. *Philos Trans R Soc London* 1838; 128:371-394.
- Ferwerda JG. *The world of 3-D: a practical guide to stereo photography*. Borger, the Netherlands: 3-D Book Productions, 1990.
- Sexton I, Surman P. Stereoscopic and autostereoscopic display systems. *IEEE Signal Processing Mag* 1999; 16:85-99.
- Getty DJ. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In: Peitgen HO, ed. *Digital mammography: IWDM 2002—6th International Workshop on Digital Mammography*. Bremen, Germany: Springer, 2002; 431-435.
- Hochberg J. *Perception. II. Space and movement*. In: Kling JW, Riggs LA, eds. *Woodworth and Schosberg's experimental psychology*. 3rd ed. New York, NY: Holt, Rinehart & Winston, 1971; 475-550.
- Goodsitt MM, Chan HP, Damer KL, Hadjiiski LM. The effects of stereo shift angle, geometric magnification and display zoom on depth measurements in digital stereomammography. *Med Phys* 2002; 29:2725-2734.
- Goodsitt MM, Chan HP, Hadjiiski L. Stereomammography: evaluation of depth perception using a virtual 3D cursor. *Med Phys* 2000; 27:1305-1310.
- Maidment ADA. Effects of quantum noise on dose and contrast sensitivity in stereoradiography. *Med Phys (in press)*.
- Samei E, Catarious DM Jr, Baydush AH, Floyd CE Jr, Vargas-Voracek R. Bi-plane correlation imaging for improved detection of lung nodules. *SPIE Med Imaging (in press)*.
- Calhoun PS, Kuszyk BS, Heath DG, Carley JC, Fishman EK. Three-dimensional volume rendering of spiral CT data: theory and method. *RadioGraphics* 1999; 19:745-764.